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ANNALS of SURGERY

A Monthly Review of
Surgical Science and Practice

Since 1885

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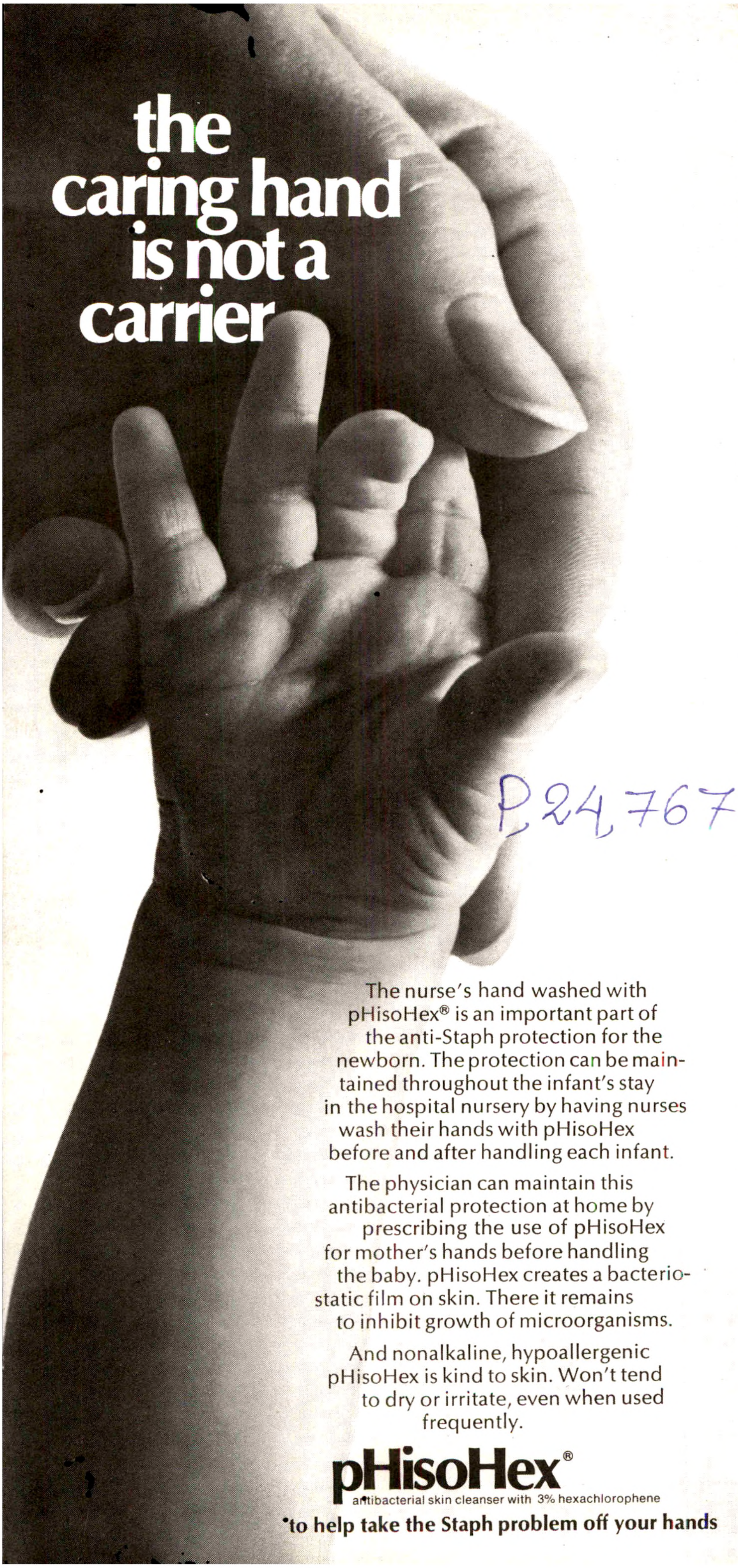

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pHisoHex contains a colloidal dispersion of hexachlorophene 3% in a stable emulsion consisting of entsufon (sodium octylphenoxyethoxyethyl ether sulfonate) 50%, petrolatum 7%, lanolin cholesterols 0.7%, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.

Actions: pHisoHex has bacteriostatic action against staphylococci and other gram-positive bacteria. Cumulative antibacterial action develops with repeated use.

Indications: pHisoHex is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. It may also be used for washing to control an outbreak of gram-positive infection in the nursery when good hospital practice has been inadequate as a total program of infection control. It should be used only as long as necessary for infection control.

Contraindications: pHisoHex should not be used on burned or denuded skin. It should not be used as an occlusive dressing, wet pack, or lotion. It should not be used routinely for prophylactic total body bathing. It should not be used as a vaginal pack or tampon, or on any mucous membranes. pHisoHex should not be used on persons with sensitivity to any of its components. It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

Warnings: Rinse thoroughly after use, especially from sensitive areas such as the scrotum and perineum.

If left in contact with burned or denuded skin or mucous membranes, sufficient hexachlorophene may be absorbed to cause toxic symptoms. Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophene absorption.

Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions.

pHisoHex should be discontinued promptly if signs or symptoms of cerebral irritability occur.

In a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on burned skin or exposure to a powder accidentally containing approximately 6.5% hexachlorophene. Examinations of brain tissue in some of these cases revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3% hexachlorophene for 90 days.

pHisoHex is intended for external use only. If swallowed, pHisoHex is harmful especially to infants and children. pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.

Precautions: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly.

Adverse Reactions: Dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

Treatment of Accidental Ingestion: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. (See Prescribing Information for detailed treatment.)

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Usage in ambulatory patients: Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Percodan should be cautioned accordingly.
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Usage in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Percodan should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.
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Treatment: Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.
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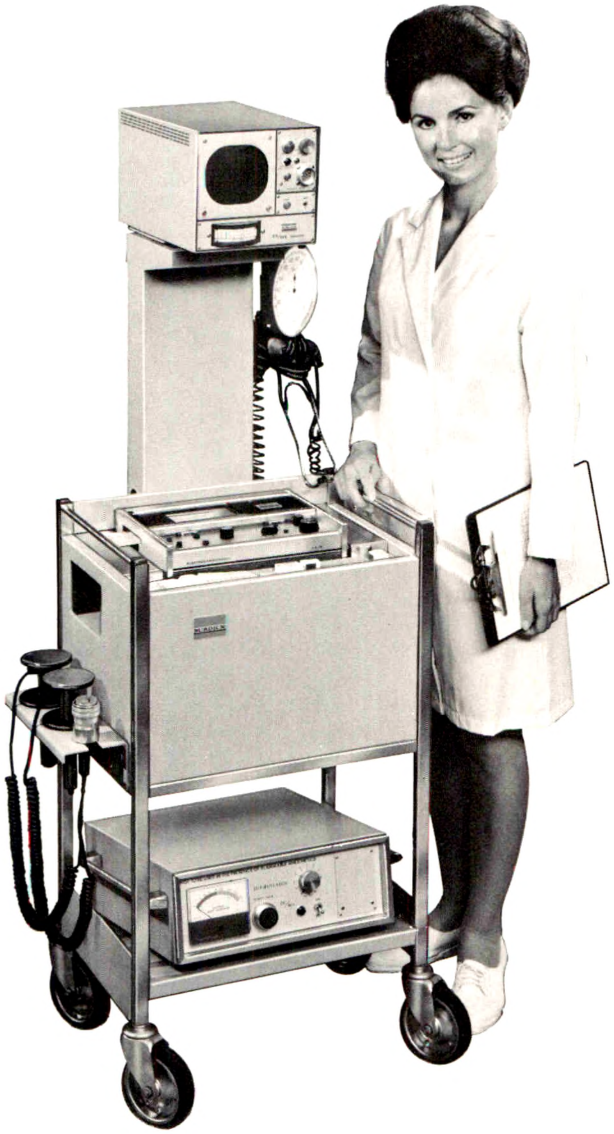

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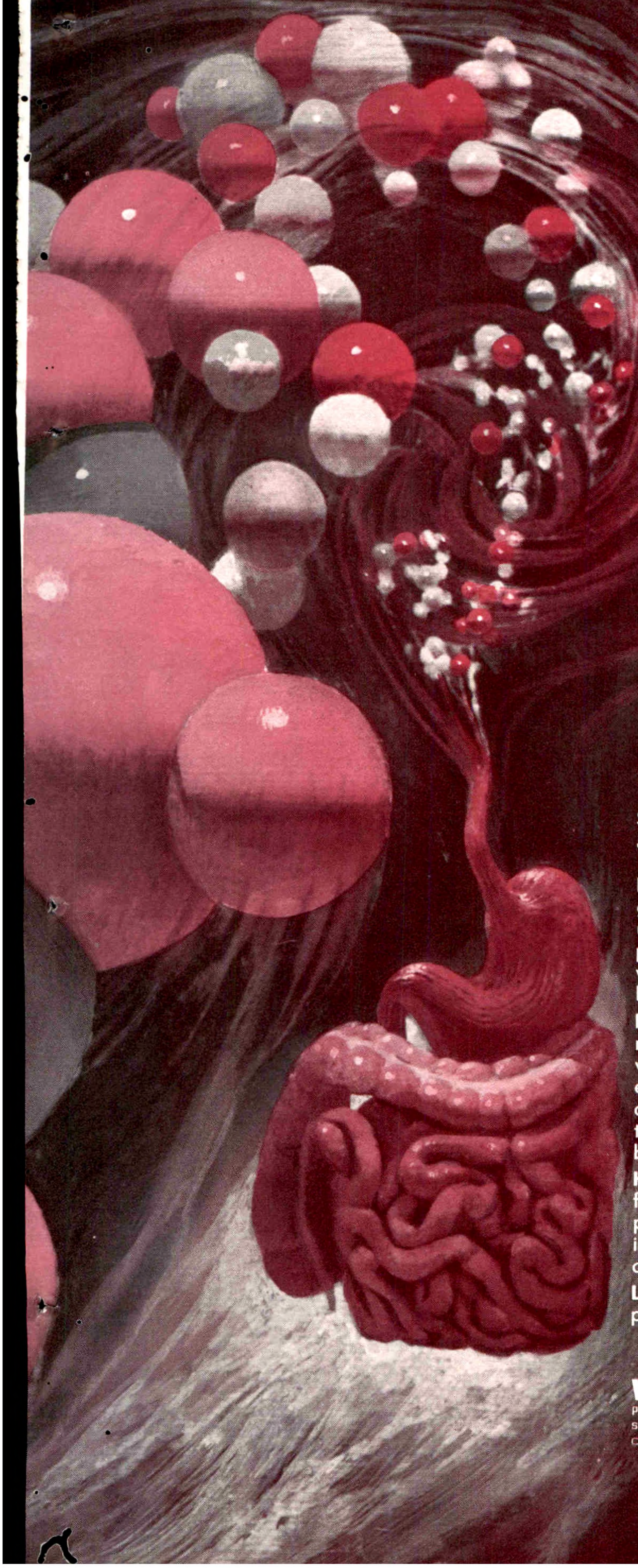

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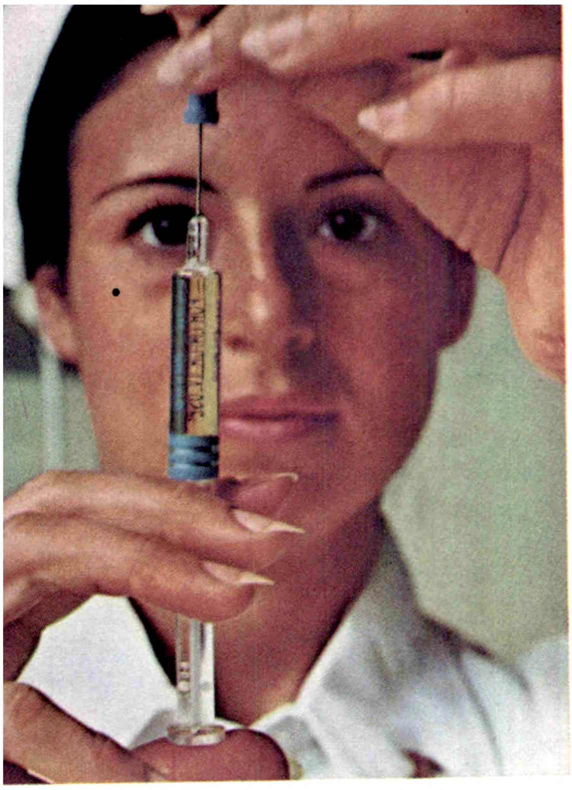
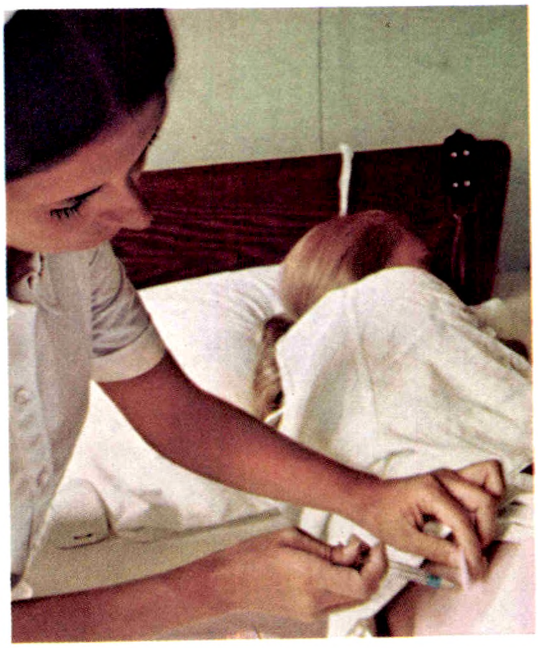
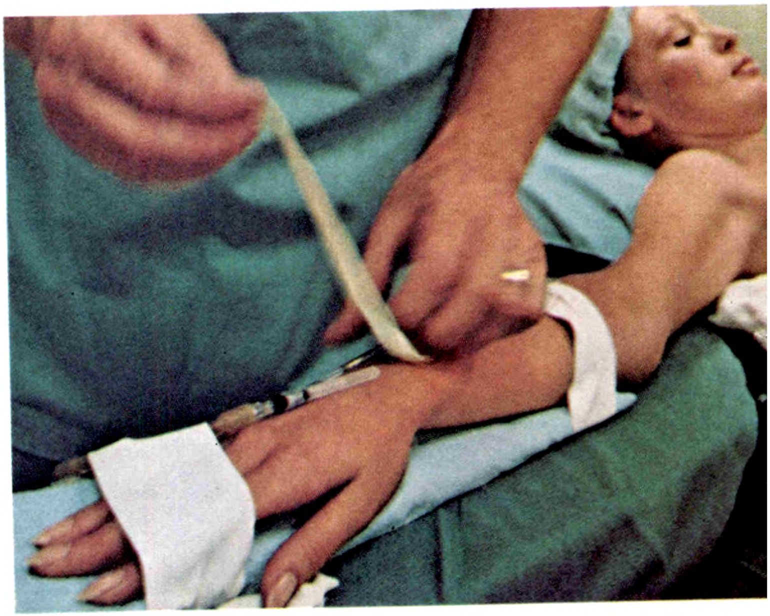
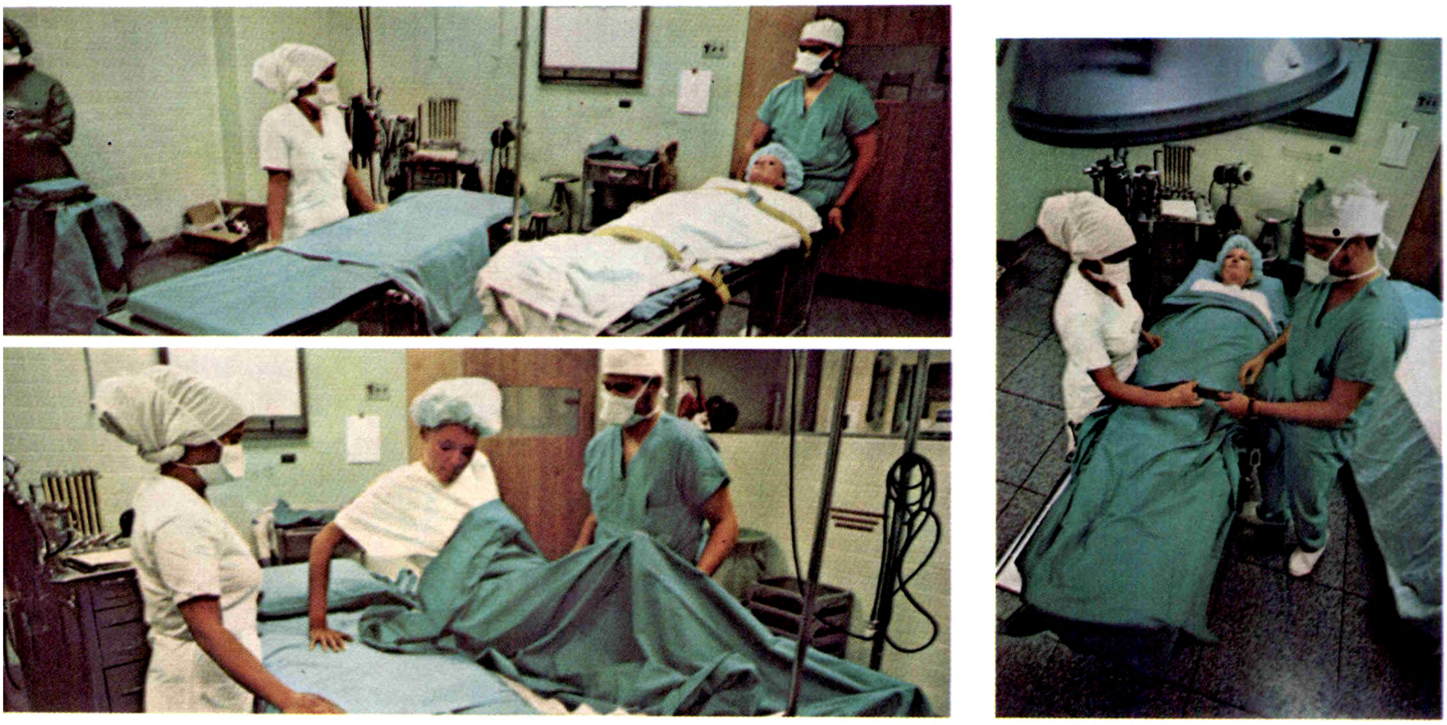




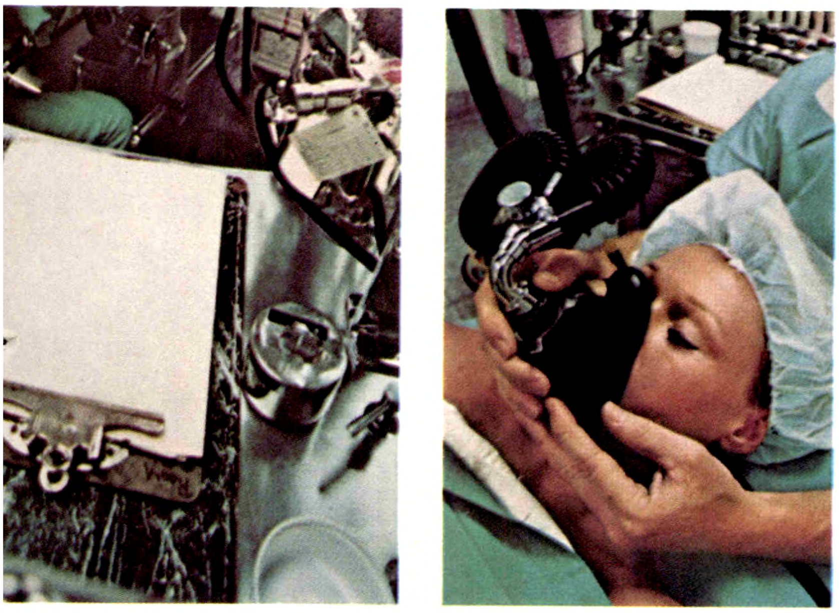
If the patient is overanxious one to two hours prior to surgery, the anxiety



Additionally, Injectable Valium (diazepam) can



can be relieved with 10 mg of Injectable Valium (diazepam) I.M.



Injectable Valium (diazepam) is a useful premedicant for reducing undue anxiety. Recall of preoperative procedures is markedly diminished. When given in conjunction with narcotics, a reduction of narcotic dosage should be considered. (See prescribing information.) Injectable Valium should not be mixed with other drugs, solutions, or fluids. The new 10-mg disposable syringe can help you observe this precaution at the same time it helps assure aseptic handling. Injectable Valium seldom significantly alters vital signs. Nevertheless, there have been infrequent reports of hypotension and rare reports of apnea and cardiac arrest, usually following I.V. administration. Resuscitative facilities should be available.

To relieve excessive preoperative anxiety, remember Injectable Valium (5 mg/ml) 2-ml ampuls, 10-ml vials, 2-ml Tel-E-Ject™ (disposable syringes).

diminish recall of the preoperative procedure.

every step of the way.

Please see the following page for a summary of product information.

Injectable Valium® (diazepam)

ready-to-use 2-ml Tel-E-Ject™ (disposable syringes)
10-ml vials
2-ml ampuls
(5 mg/ml)

Can ease undue preoperative tension and anxiety.
Calming effect is usually prompt and pronounced.
Induces satisfactory or light sleep, from which patient is easily aroused to follow instructions.
Rarely produces significant changes in vital signs.
Can reduce recall of procedure.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus and severe recurrent seizures; anxiety prior to gastroscopy, esophagoscopy, and surgical procedures; cardioversion (I.V.).

Contraindicated: In infants; in patients with known hypersensitivity to the drug; in acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *Inject I.V. slowly, directly into vein; take at least one minute for each 5 mg (1 ml) given. Do not mix or dilute with other solutions or drugs. Do not add to I.V. fluids.* Rare reports of apnea or cardiac arrest noted, usually following I.V. administration, especially in elderly or very ill and those with limited pulmonary reserve; duration is brief; resuscitative facilities should be available. Not recommended as sole treatment for psychotic or severely depressed patients. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. Caution against hazardous occupations requiring complete mental alertness. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard to mother and child.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects – particularly with known compounds which may potentiate action of Valium, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Not recommended for bronchoscopy, laryngoscopy, obstetrical use, or in diagnostic procedures other than gastroscopy and esophagoscopy. Laryngospasm and increased cough reflex are possible during gastroscopy; necessary countermeasures should be available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Since effect with narcotics may be additive, appropriate reduction in narcotic dosage is possible. Use lower doses (2 to 5 mg) for elderly and debilitated. Safety and efficacy in children under 12 not established.

Side Effects: Drowsiness, fatigue, ataxia, confusion, depression, constipation, dysarthria, diplopia, headache, hypoactivity, hiccups, hypotension, incontinence, jaundice, nausea, changes in libido, changes in salivation, phlebitis at injection site, urinary retention, skin rash, syncope, slurred speech, urticaria, tremor, vertigo, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial adult dose is 2 to 10 mg I.M. or I.V., depending on indication for use. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Precautions and Adverse Reactions.) In gastroscopy and esophagoscopy, 5 to 10 mg, I.M. or I.V., 30 min. prior to procedure. As preoperative medication, 10 mg, I.M., 1 to 2 hours before surgery. In cardioversion, 5 to 15 mg, I.V., within 5 to 10 min. prior to procedure. Give I.V. injections slowly; take at least 1 minute for each 5 mg (1 ml).

In acute conditions, injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory; not more than 30 mg should be given within 8-hour period. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Supplied: Valium® (diazepam) Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject™ (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam, compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

The controversial adenoma

One of the most common lesions of the GI tract. Often asymptomatic. Often an indication of the presence and/or development of more polyps. It has a much-debated relationship to colonic cancer. Some think it actually degenerates into a carcinoma. Some think not. When polyps are present in the distal colon, the best way to find them is through conventional sigmoidoscopic examination. And, be they benign or malignant, the best therapy is removal.

Many surgical procedures can contribute to temporary postoperative constipation. To help return bowel function to normal as quickly and as gently as possible, consider FLEET ENEMA for postoperative constipation relief.

- Works rapidly, usually within 2 to 5 minutes
- Cleanses the left colon and rectum; spares upper portions of the GI tract
- Ready to use, easy to use, completely disposable
- Unique construction regulates flow; prevents leakage and reflux
- Anatomically correct, prelubricated rectal tip helps avoid injury to bowel wall

Fleet® Enema

Fast, effective relief of postoperative constipation

Artist's conception.

Contraindications: Do not use when nausea, vomiting, or abdominal pain is present. **Warnings:** Frequent or prolonged use of enemas may result in dependence. Take only when needed or when prescribed by a physician. **Precautions:** Do not administer to children under two years of age unless directed by a physician.

FREE BOOKLET. A supply of a patient booklet, *Protecting Yourself with a "Procto" Examination,* is available, free of charge, on request to C. B. FLEET CO., INC., P. O. Box 1100, Lynchburg, Va. 24505.

Fleet® BRAND pharmaceuticals

C. B. FLEET CO., INC.
Lynchburg, Va. 24505

F3A73

For surgeons who believe in bikinis.

Nowadays, no matter where the incision, the scar is likely to be on public view. Help make it a beautiful one with the aid of PROLENE Suture, the monofilament whose smoothness is a

Indications—PROLENE Polypropylene Suture, U.S.P., may be used wherever Nonabsorbable Surgical Suture, U.S.P., is recommended. **Contraindications**—There are no known contraindications. **Warning**—Unused PROLENE Polypropylene Sutures may not be resterilized more than three times by the standard autoclaving method without loss of strength. **Precaution**—As with other synthetic sutures, knot security requires the standard surgical technic of flat and square ties, with additional throws if indicated by surgical circumstance and the experience of the operator. **Adverse Reactions**—Minimum transitory reactions have been reported.

The most important step in maintaining shock reversal is restoring tissue perfusion

The consequences of decreased capillary perfusion can be far-reaching, as sludging in the microcirculation may seriously diminish oxygen availability to the vital organs.

Rheomacrodex decreases red blood cell aggregation to a greater extent than crystalloids, blood or plasma.[4-8] The resulting improvement in microcirculatory blood flow is reflected in increased oxygen availability and consumption, a vital contribution to the reversal of shock.[9]

With Rheomacrodex, you can expect a profile of rapid hemodynamic improvement: increased cardiac output,[8, 10-13] reduced peripheral resistance,[8, 10-13] lowered mean transit time,[10] and a rise in central venous pressure.[10-13]

In addition to these clinical benefits, Rheomacrodex offers immediate availability and low cost.

Blood volume expansion. Restoration of microcirculatory blood flow. They're both critically important to survival in shock. Consider the volume expander that offers both.

See brief summary on following page.

Artist's rendering of erythrocyte aggregation similar to that encountered in shock.

Typical dispersion of aggregates following Rheomacrodex infusion.

Rheomacrodex®
(dextran 40)

Works two important ways at once.

Pharmacia

Rheomacrodex®
(dextran 40)

Contraindications: Marked thrombocytopenia, hypofibrinogenemia or renal disease with severe oliguria or anuria.
Warnings: Since dextran-40 draws water from extravascular space, dehydrated patients should be given additional fluids. The degree of dehydration can be assessed by serum or urine osmolarity tests. Diuretics may be used to maintain adequate urine flow. Renal failure, osmotic nephrosis and, occasionally, abnormal hepatic and renal function values have been reported. Because safety in early pregnancy has not been established, do not use in women of childbearing age unless potential benefits outweigh risks. Use with caution in patients with active bleeding, because improved perfusion pressure and flow may cause further blood loss.
Precautions: Dosages above 20 ml./kg. may prolong bleeding time. To avoid excess dosage with circulatory overloading, monitoring of central venous pressure is recommended. Do not depress hematocrit below 30 vol.%.
Because the presence of Rheomacrodex can interfere with bilirubin and protein assays, blood glucose determinations, and some blood typing and cross matching procedures, it is recommended that blood samples for these tests be drawn prior to infusion of Rheomacrodex or that the lab be informed that Rheomacrodex has been administered so that suitable assay methods be applied.
Adverse Reactions: Mild urticaria has occurred in a few patients. More severe allergic reactions including generalized urticaria, tightness of chest, wheezing, hypotension, nausea and vomiting may occur rarely. They may be relieved by parenteral epinephrine, ephedrine or antihistamines.
Dosage: Total dosage should not exceed 20 ml./kg. in the first 24 hours or 10 ml./kg. in each subsequent 24 hours. Do not continue beyond 5 days.
Supplied: Bottles of 500 ml. 10% solution in normal saline or in 5% aqueous dextrose.

References:
1. Ahnefeld, F.W., Halmagyi, M., and Uberla, K.: Anaesthesist 14:137 (May) 1965. **2.** Gruber, U.F., Meili-Gerber, E., Grass, S., and Allgower, M.: Proc 10th Cong Int Soc Blood Transf, 1965, pp. 1116-1119. S. Karger, Basel (Switzerland). **3.** Gruber, U.F., Bergentz, S.E., and Fritjofsson, A.: Symposium on Rheomacrodex I (1964), pp. 13-23. **4.** Mainardi, L.C., Bhanganada, K., Mack, J.D., and Lillehei, C.W.: Surgery 56:349 (Aug.) 1964. **5.** Martinovic, N., and Melrose, D.: J Cardiovasc Surg 4:610 (Aug.) 1963. **6.** Suzuki, F., Baker, R.J., and Shoemaker, W.C.: Ann Surg 160-263 (Aug.) 1964. **7.** Baker, R.J., St. Ville, J.M., Suzuki, F., and Shoemaker, W.C.: Arch Surg 90:538 (Apr.) 1965. **8.** Baker, R.J., Shoemaker, W.C., Suzuki, F., Freeark, R.J., and Strohl, E.L.: Arch Surg 89:373 (Aug.) 1964. **9.** Mohr, P.A., Monson, D.O., Owczarski, C., and Shoemaker, W.C.: Circulation 39:379 (1969). **10.** Carey, J.S., Woodward, N.W., Mohr, P.A., Suzuki, F., Brown, R.S., Baker, R.J., and Shoemaker, W.C.: Surg Gynec Obstet 121:563 (Sept.) 1965. **11.** Carey, J.S., Brown, R.S., Woodward, N.W., Yao, S.T., and Shoemaker, W.C.: Surg Gynec Obstet 121:1059 (Nov.) 1965. **12.** Cohn, J.N., Luria, M.H., Daddario, R.C., and Tristani, F.E.: Circulation 35:316 (Feb.) 1967. **13.** Cohn, J.N., and Luria, M.H.: Arch Intern Med 116:562 (Oct.) 1965.

PHARMACIA LABORATORIES INC.
Piscataway, New Jersey 08854

Pharmacia

Tablets
Darvon-N™ with A.S.A.®

Each tablet contains 100 mg. propoxyphene napsylate and 325 mg. aspirin.

Tablets
Darvon-N™

Lilly
200642

Each tablet contains 100 mg. propoxyphene napsylate.

Indication: For the relief of mild to moderate pain.

Contraindications: Hypersensitivity to propoxyphene and, in the combination product, to aspirin.

This agent should not be used in children, since adequate data to establish safe conditions of use are lacking.

Warnings: Propoxyphene napsylate may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

Salicylates should be used with caution in the presence of peptic ulcer.

Use in Pregnancy—The safety of the use of this agent during pregnancy has not been established.

Drug Dependence—Tolerance, psychological dependence, and physical dependence have been reported; the abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less. Propoxyphene will not support morphine dependence.

Precautions: Patients who have received narcotic drugs for long periods of time may have developed physical dependence, and the sudden substitution of ordinary doses of propoxyphene napsylate may result in an acute withdrawal syndrome. These symptoms may be avoided by gradually reducing the dose of the prior medication as propoxyphene napsylate is substituted for pain relief.

Salicylates present in Darvon-N™ with A.S.A.® (propoxyphene napsylate with aspirin, Lilly) may enhance the effect of anticoagulants and inhibit the uricosuric effect of probenecid. In large doses, salicylates may also decrease Insulin requirements.

Adverse Reactions: Dizziness, headache, sedation, somnolence, paradoxical excitement, insomnia, skin rashes, and gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, and constipation) may occur with the recommended doses of propoxyphene. Euphoria may occasionally occur.

Salicylates present in the combination product may induce hypersensitivity, urate kidney stones, chronic gastro-intestinal blood loss, tinnitus, nausea, and vomiting.

[012772]

Additional information available to the profession on request.

Eli Lilly and Company, Indianapolis, Indiana 46206

relief from
mild to moderate
postsurgical pain...

a logical step-down
from injectable
analgesics...

Tablets
Darvon-N™ with A.S.A.®
100 mg. propoxyphene napsylate and 325 mg. aspirin

Lilly

*Please see adjoining column
for prescribing information.*

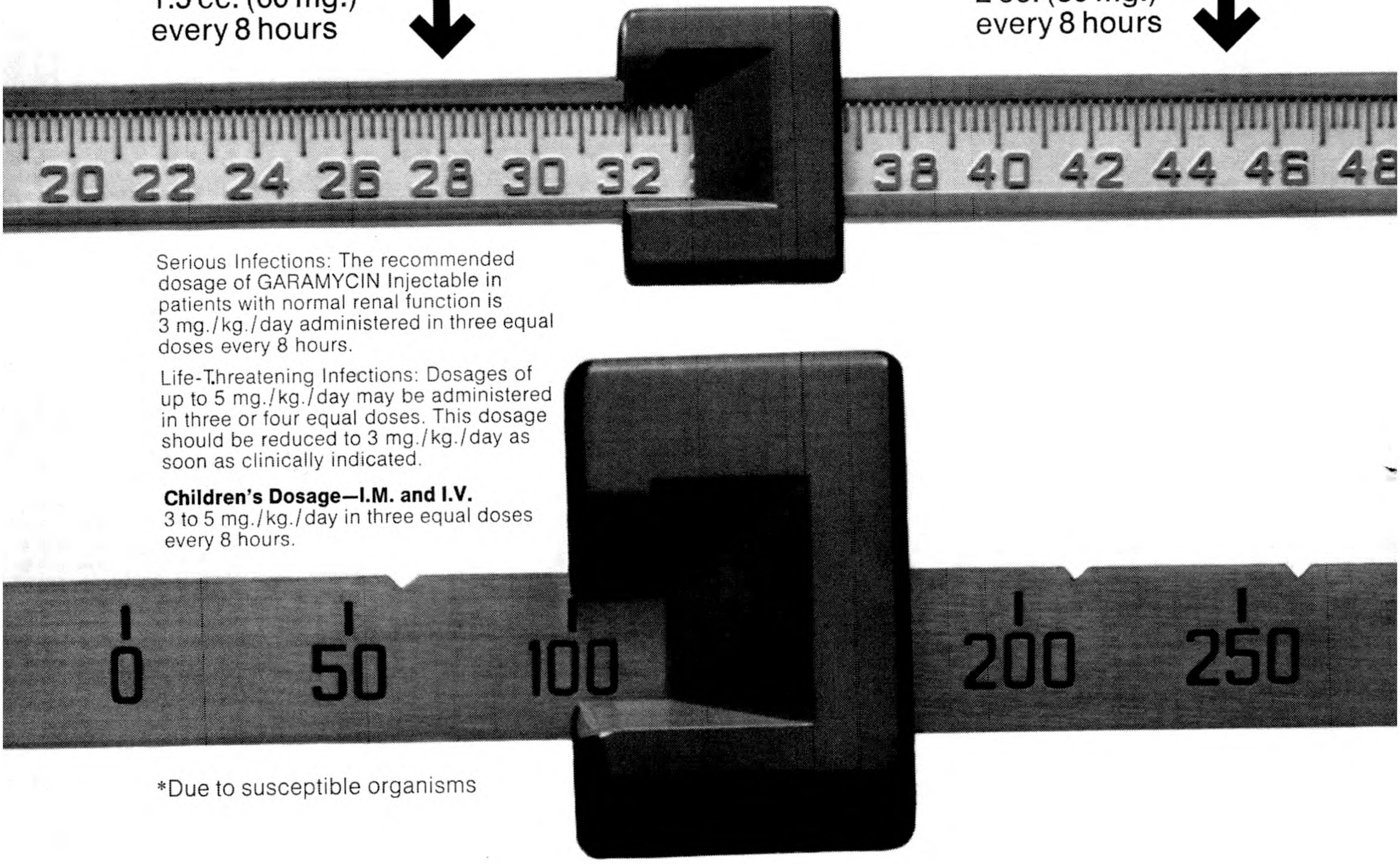
In serious gram-negative infections*

Simplified dosage guidelines

Usual adult dosage--I.M. and I.V.--in patients with normal renal function

132 lbs. or less
1.5 cc. (60 mg.)
every 8 hours

Over 132 lbs.
2 cc. (80 mg.)
every 8 hours



Serious Infections: The recommended dosage of GARAMYCIN Injectable in patients with normal renal function is 3 mg./kg./day administered in three equal doses every 8 hours.

Life-Threatening Infections: Dosages of up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

Children's Dosage—I.M. and I.V.
3 to 5 mg./kg./day in three equal doses every 8 hours.

*Due to susceptible organisms

WARNING
Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

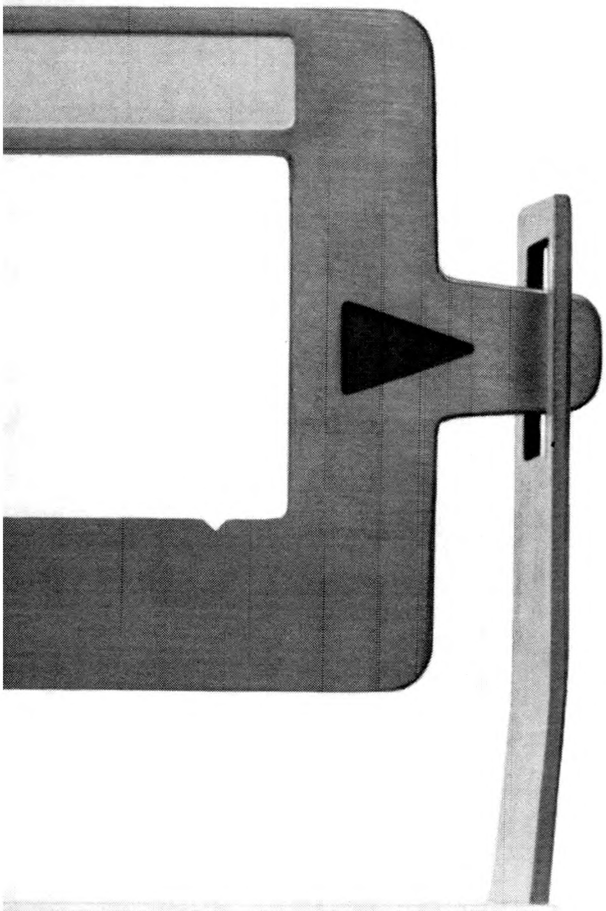
Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly strepto-

Schering

Garamycin®
gentamicin sulfate injectable
I.M./I.V.

40 mg. per cc.

Each cc. contains gentamicin sulfate
equivalent to 40 mg. gentamicin



Duration of therapy—I.M. and I.V.

The usual duration of treatment is 7 to 10 days. In difficult and complicated infections, a longer course of therapy may be necessary.

Instructions for I.V. use

Dilution—A single dose is diluted in 100 or 200 cc. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution should not exceed 1 mg./cc. (0.1%).

Infusion time—The solution is infused over a period of 1 to 2 hours.

Premixing—GARAMYCIN Injectable should not be physically premixed with other drugs but should be administered separately in accordance with the recommended route of administration and dosage schedule.

In adults with impaired renal function

The single dose of GARAMYCIN Injectable given by patient weight remains the same; however, the interval between doses must be extended.

This interval may be approximated by multiplying the serum creatinine by eight as follows:

Serum creatinine × 8 = frequency of administration
(mg./100 ml.) (in hours)

This dosage schedule is not intended as a rigid recommendation, but is provided as a guide to dosage when the measurement of gentamicin serum levels is not feasible.

See Clinical Considerations section which follows...

**ycin, neomycin, kanamycin, cephaloridine, omycin, polymyxin B, and polymyxin E olistin), should be avoided.
The concurrent use of gentamicin with po- nt diuretics should be avoided, since certain uretics by themselves may cause ototoxic- . In addition, when administered intrave- usly, diuretics may cause a rise in gentami- n serum level and potentiate neurotoxicity.
SAGE IN PREGNANCY Safety for use pregnancy has not been established.**

Schering

Garamycin® Injectable
brand of gentamicin sulfate U.S.P., injection, 40 mg./cc.
Each cc. contains gentamicin sulfate equivalent to 40 mg. gentamicin
For Parenteral Administration

WARNING: Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause toxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), **Escherichia coli** and **Klebsiella-Enterobacter-Serratia** species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin type drug is usually indicated as concomitant antimicrobial therapy.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:

PATIENTS WITH NORMAL RENAL FUNCTION*

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb.), the usual dosage is 80 mg. (2 cc.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dose is 60 mg. (1.5 cc.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

*In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration, in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 cc. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution, in both instances should normally not exceed 1 mg./cc. (0.1%). The solution is infused over a period of 1 to 2 hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically pre-mixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per cc., 2 cc. multiple-dose vials for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per cc., 2 cc. multiple-dose vials for parenteral administration. APRIL, 1972
AHFS Category 8:12.28

For more complete prescribing details, consult Package Insert or Physicians' Desk Reference. Schering literature is also available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033. SLR-192

Garamycin®
gentamicin sulfate
injectable
I.M./I.V.

40 mg. per cc.

Each cc. contains gentamicin
sulfate equivalent to 40 mg. gentamicin

Description: Keflin® (sodium cephalothin, Lilly) is a semisynthetic cephalosporin antibiotic for parenteral use. It is the sodium salt of 7-(thiophene-2-acetamido) cephalosporanic acid. The sodium content is 55 mg. per Gm. of cephalothin.

Actions: The bactericidal action of cephalothin results from inhibition of cell-wall synthesis. In-vitro and in-vivo activity has been demonstrated against strains of the following micro-organisms:

- *Staphylococcus aureus* (penicillin-sensitive and penicillinase-producing)
- Beta-hemolytic and other streptococci (many strains of enterococci, e.g., *Streptococcus faecalis,* are relatively resistant)
- Pneumococci
- Clostridia
- *Hemophilus influenzae*
- *Neisseria gonorrhoeae*
- *Escherichia coli* and other coliform bacteria
- *Klebsiella-Aerobacter* sp.
- *Proteus*
- *Salmonella* sp.
- *Shigella* sp.

Indications: Keflin is indicated in the treatment of serious infections of the respiratory tract, genito-urinary tract, soft tissue and skin, gastro-intestinal tract, bones and joints, bloodstream, and cardiovascular system due to susceptible organisms. Also, it has beeh effective in cases of peritonitis, septic abortion, and staphylococcus and pneumococcus meningitis. Effectiveness has not been established in other types of meningeal infection.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Keflin.

Contraindication: Keflin is contraindicated in persons who have shown hypersensitivity to cephalosporin antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS. INSTANCES OF PATIENTS WHO HAVE HAD SEVERE REACTIONS TO BOTH DRUGS, INCLUDING DEATH FROM ANAPHYLAXIS, HAVE BEEN REPORTED.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exception should be made with regard to Keflin.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions: Patients should be followed carefully so that any side-effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keflin occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine, antihistamines, pressor amines, or corticosteroids).

When Keflin is administered to patients with transient or persistent reduction of urinary output due to impaired renal function, the total daily dose should be reduced. Careful clinical observation and laboratory studies should be made, because higher and more prolonged systemic antibiotic concentrations can occur (*see* Administration and Dosage below).

When intravenous doses of cephalothin larger than 6 Gm. daily are given by infusion for periods longer than three days, they may be associated with thrombophlebitis, and the veins may have to be alternated. The addition of 10 to 25 mg. of hydrocortisone to intravenous solutions containing 4 to 6 Gm. of cephalothin may reduce the incidence of thrombophlebitis. The use of small I.V. needles in the larger available veins may be preferred.

Prolonged use of Keflin® (sodium cephalothin, Lilly) may result in the overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

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Adverse Reactions: *Hypersensitivity*—Maculopapular rash, urticaria, reactions resembling serum sickness, and anaphylaxis have been reported. Eosinophilia and drug fever have been reported as associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

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ANNALS OF SURGERY

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Regional Lymphatics and Cancer Immunity

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THE REGIONAL LYMPH NODES have long been considered the "seat" of specific immune responsiveness.[4] With the increasing evidence of immunologic factors associated with the initiation and progression of both human and animal tumors, much recent attention has been focused on the role of the regional lymphatic system in the expression of host ability to resist tumor growth.[1,6,8,10,11,12,19] Following Mitchison's demonstration in the early '50's that cells from the regional lymph nodes are capable of adoptively transferring immunity to tumor allografts, an important immunologic role of nodal tissue was first established.[15,16] More recently, it has been demonstrated that regional lymph node cells from appropriately immunized syngeneic animals are also capable of transferring immunity to tumor-specific transplantation antigens (TSTA).[1] Immunocompetent cells from other lymphoid organs, such as the spleen, however, are also capable of conferring such immunity, demonstrating that the host immune response is not completely confined to the regional lymphatic system.[2]

Attempts to define the consequence of regional lymphadenectomy on the host-tumor relationship have met with conflicting results.[1,6,8,11,12] A recognized shortcoming of the experimental model has been the unreliability of assuming that once the regional nodes are removed, their functional capacity is not fulfilled by other immunocompetent organs (*e.g.*, spleen, which, as mentioned, is also capable of adoptively transferring tumor-specific immunity, or other nodes implicated by collateral lymphatic channels). In order to obviate this potential difficulty, a model of complete afferent lymphatic disruption has been applied to a syngeneic tumor system. By this technic we have demonstrated that the regional lymphatics play an essential role in the early recognition of tumor-specific antigens. With progressive tumor growth, however, even in the presence of persistent afferent lymphatic interruption, host sensitization is possible. Based upon these experimental findings further confirmation suggesting a critical role of the regional lymphatic system in tumor immunity is presented.

Materials and Methods

Tumor-Host System

Inbred, adult, Sewall-Wright strain 2 female guinea pigs obtained from the Animal Production Unit of the National Institutes of Health were used. First and second set skin grafts within this strain are permanently accepted. Animals were age-matched and housed six in a cage with Wayne guinea pig chow and water available *ad libitum*. The tumor employed was a liposarcoma, designated MCA-A, induced in an adult, female strain 2 guinea pig by the subcutaneous injection of 4 mg of methylcholanthrene. The MCA-A sarcoma has been maintained by serial transplantation into female strain 2 guinea pigs and was used in its seventh through ninth transplant generations. The tumor has previously been shown to contain tumor-specific transplantation antigens[13] according to the method of Prehn and Main.[17]

Preparation of Tumor Cell Suspension

Single tumor cell suspensions were prepared by a modification of the method of Madden and Burk.[14] Tumor tissue was trimmed of necrotic debris and fibrous tissue and finely minced with scissors. The tumor frag-

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ments were placed in trypsinizing flasks where enzymatic dissociation into a single cell preparation was carried out using Gey's solution containing 0.25% trypsin. The mixture was agitated on a magnetic stirrer for 20 minutes at 37°C, resuspended and washed three times in RPMI 1640 media containing penicillin, streptomycin, and 20% fetal calf serum. The final cell button was resuspended in media RPMI 1640 containing 20% fetal calf serum and the number of viable cells quantitated in a hemocytometer by determining the amount of cells excluding 0.05% trypan blue. Viability of single cell preparations ranged from 85 to 95%. The cells were then resuspended in media 1640 with 20% fetal calf serum and the final concentration adjusted so that 0.05 ml. contained the desired number of viable tumor cells. 1×10^3 viable tumor cells was determined to be the minimal cell inoculum which produced a tumor in 100% of animals when injected intramuscularly; intradermal inoculation, however, required 1×10^7 or more viable tumor cells in order to produce a progressively growing tumor.

Experimental Model

Using our own modification of a procedure devised by Frey and Wenk,[9] and later applied to skin allografting experiments by Baker and Billingham,[3] circular, full-thickness skin pedicles approximately 2 cm. in diameter and containing the panniculus carnosus muscle were cut from the shaved flanks of ether-anesthetized female strain 2 guinea pigs. A prominent neurovascular stalk supplying the isolated segment of flank skin, and comprised of a perforating intercostal artery and vein with some adjacent neural fibers, was identified and isolated. All adherent areolar tissue and any connecting lymphatic fibers were sharply excised. The resulting circular skin defect was then closed longitudinally with interrupted 3-0 nylon sutures, leaving a small central aperture for emergence of the vascular pedicle. A double sterile sheet of Adaptic non-adherent dressing (Johnson and Johnson, New Brunswick, New Jersey) with a central slit to accommodate the vascular stalk was placed over the wound and under the raw surface of the skin flap. The pedicle was then repositioned on the flank and stabilized with surrounding adhesive tape. Intradermal inoculation of the pedicle with the single cell tumor preparation was performed using a #27 gauge needle on a tuberculin syringe. An additional sterile dressing of Telfa (Kendall, Chicago, Illinois) was applied with several strips of adhesive tape. The dressing allowed normal mobility and protection of the pedicle from cannibalization. Meticulous dressing changes, initially daily and thereafter less frequently, were necessary to assure good viability of the pedicle with no chance for reattachment. Thrice weekly inspection and palpatation of the pedicles were employed to determine the time of initial tumor appearance. Following this, frequent measurement of the two largest perpendicular diameters of the tumor was performed. After each inspection, careful redressing was performed. Determination of the adequacy of lymphatic interruption in this model has previously been reported.[10]

Selected amputations of growing pedicle-tumors were performed by sharply excising the arteriovenous nutrient vessels and removing the tumor containing skin pedicle. Minimal bleeding was controlled with pressure and the small wound was dressed open. Those animals whose pedicle-tumors were amputated were rechallenged with isologous MCA-A tumor either intradermally, or in a new alymphatic skin pedicle fashioned in an identical manner on the contralateral flank. In order to determine the extent of concomitant immunity in the presence of actively growing tumors, selected animals with an intact pedicle-tumor received an additional tumor cell challenge in a second alymphatic skin pedicle constructed on the contralateral flank. Similar dressing care and inspection was employed in all situations.

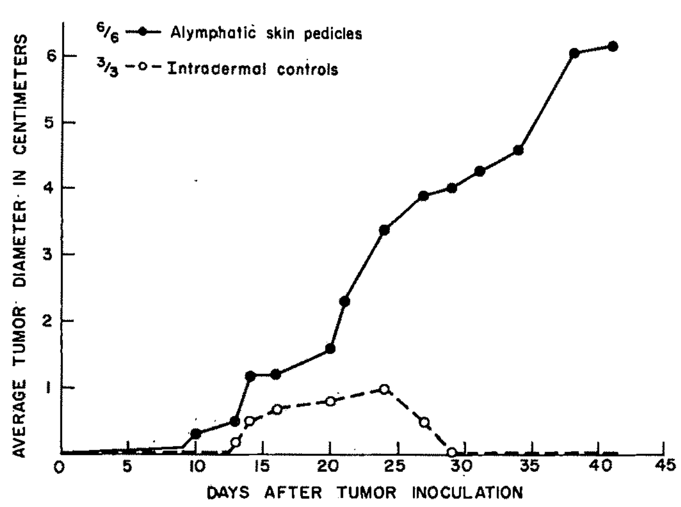

Fig. 1. Growth of 1×10^6 MCA-A tumor cells in alymphatic skin pedicles compared to the intact skin of syngeneic strain 2 guinea pigs.

Experiments and Results

Experiment 1. Tumor Growth in Normal Skin vs. Growth in Skin Deprived of Afferent Lymphatic Drainage.

Previous work in our laboratory has shown that as many as 5 million viable MCA-A tumor cells are rejected by normal syngeneic strain 2 animals when given intradermally. In order to determine the number of viable MCA-A tumor cells necessary to initiate progressive tumor growth in an area of skin devoid of afferent lymphatic drainage, a series of animals was randomly in-

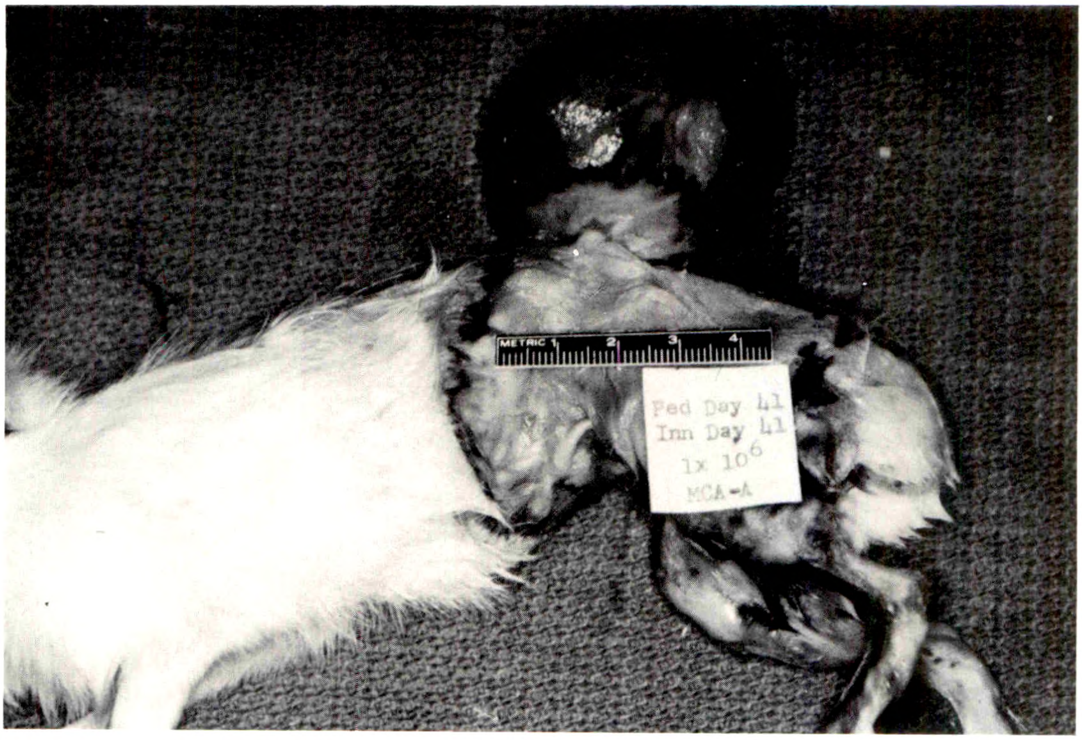

FIG. 2. Photograph of alymphatic skin pedicle in a strain 2 guinea pig 41 days after inoculation with 1 × 10^6 MCA-A tumor cells.

oculated with varying tumor doses either intradermally in the intact flank or intradermally in an "alymphatic skin pedicle." Animals receiving 1 × 10^6 viable MCA-A cells in the intact skin developed small tumors averaging 1 cm. in diameter on day 24, but which were completely rejected by day 29 with no tumor residual. When the same tumor inoculum (1 × 10^6) was given in the skin pedicle devoid of afferent lymphatic drainage, progressive tumor growth resulted, averaging greater than 6 cm. diameter on day 41 (Figs. 1 and 2). All animals with pedicle-tumors were dead by day 64 and autopsies revealed no evidence of distant metastases. Likewise, 5 × 10^5 viable MCA-A tumor cells grew progressively resulting in death of the animal when given in an "alymphatic skin pedicle" although this inoculum normally did not result in a palpable tumor when given intradermally in the intact flank with normal lymphatic drainage (Fig. 3). 1 × 10^4 viable MCA-A cells grew neither in the intact skin (0/4), nor in "alymphatic skin pedicles" (0/4).

Experment 2. Tumor-Specific Immunity Following Amputation of Alymphatic Pedicle-Tumors.

A separate series of experiments was performed to determine if animals with progressively growing alymphatic pedicle-tumors were sensitized to the MCA-A tumor specific transplantation antigens (TSTA) at some point during tumor growth (Fig. 4). Twenty days following inoculation of 1 × 10^6 MCA-A cells into the alymphatic skin pedicles the tumor-bearing pedicles of 12 animals were amputated (average tumor size at the time of amputation = 1.2 cm. diameter). Six additional animals received this cell dose in normal skin with intact lymphatics and again completely rejected the cells with no tumor residual. One week following pedicle-tumor amputation (27 days following initial inoculation) all animals were rechallenged with 1 × 10^6 viable tumor cells, either intradermally or in a second alymphatic skin pedicle constructed on the contralateral flank. None of the animals previously bearing pedicle-tumors developed new tumors when rechallenged (0/12), regardless of whether the rechallenge was in a new alymphatic skin pedicle (0/4) or intradermally in an area with intact lymphatics (0/8). The animals previously rejecting the intradermal tumor inoculation were also immune to rechallenge (0/6), while non-immune control animals receiving 1 × 10^6 viable tumor cells in alymphatic skin pedicles grew progressive tumors (3/3) and those receiving the same tumor inoculum in the intact skin grew 1 cm. tumors which again completely regressed (3/3).

Experiment 3. Establishment of the Existence of an Intact Efferent Immune Arc.

Having established that the "alymphatic pedicle-tumors," although capable of progressive lethal growth, were nevertheless capable of sensitizing the host to the MCA-A tumor-specific transplantation antigens, experiments were performed to determine if the efferent arc of the immune response remained intact. Alymphatic skin pedicles were constructed on six animals and inocu-

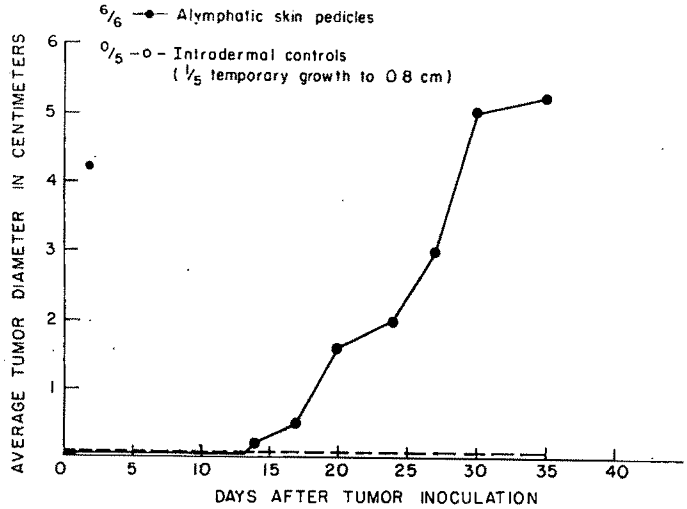

Fig. 3. Growth of 5 × 10^5 MCA-A tumor cells in alymphatic skin pedicles compared to the intact skin of syngeneic strain 2 guinea pigs.

lated with 1 × 10^6 viable MCA-A cells. Concurrent with the pedicle inoculation three of the animals received an intradermal inoculation of the same number of viable MCA-A tumor cells in the contralateral flank in an area with intact lymphatics. These three animals were protected against pedicle-tumor growth (0/3) while those receiving no intradermal tumor cells grew large pedicle-tumors (3/3) (Table I). The three animals with progressively growing pedicle-tumors were used to test for the presence of concomitant immunity as depicted in the following experiment.

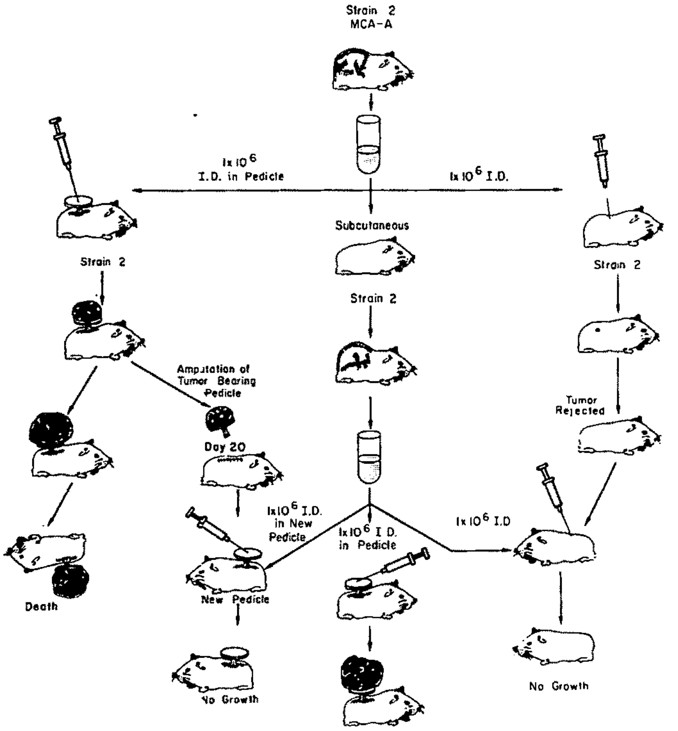

Fig. 4. Diagrammatic scheme of experiment 2 demonstrating immunity to MCA-A tumor challenge in syngeneic animals bearing a pedicle tumor for 20 days as well as animals previously rejecting an intradermal tumor.

Experiment 4. Concomitant Immunity

From experiment 2 we had previously determined that amputation of the tumor-bearing pedicles on day 20 rendered the animals immune to rechallenge with the same MCA-A tumor. To determine if animals exhibited concomitant immunity with pedicle-tumors still intact, alymphatic skin pedicles were constructed on the contralateral flank of the three animals from the previous experiment with progressively growing pedicle-tumors 25 days following initial inoculation (average tumor diameter = 1.8 cm). Each new pedicle was inoculated with 1 × 10^6 viable MCA-A tumor cells. Three additional animals not previously inoculated served as controls and received 1 × 10^6 MCA-A cells in an alymphatic skin pedicle. None of the animals with initial pedicle-tumors developed a tumor in the second pedicle (0/3), although the original tumor continued to grow at the usual rate. Each of the non-immune animals again developed large progressively growing pedicle tumors (3/3) (Table 2).

Discussion

These studies demonstrate that the regional lymphatics, although essential in the early host recognition of tumor-specific transplantation antigens (TSTA), are not necessary for the eventual development of tumor-specific immunity. In the absence of afferent lymphatic drainage a quantitative intradermal inoculum of tumor cells (*e.g.*, 1 × 10^6 MCA-A) which is normally rejected by a syngeneic host will grow progressively, resulting in death of the animal. One half this number of tumor cells (5 × 10^5), while usually resulting in no palpable tumor when inoculated into an intradermal site with normal lymphatic drainage is also capable of progressive lethal tumor growth when inoculated into an area with interrupted lymphatic continuity. The fact that the animals eventually develop tumor-specific immunity to rechallenge with isologous tumor despite the persistent growth of tumor in a region devoid of its afferent lymphatics, suggests that by the time most tumors are clinically detectable, the host's immunologic response to TSTA is no longer dependent on the regional lymph nodes. Systemic sensitization probably occurs without the necessity of intact local lymph nodes by circulation of immunocompetent cells through the tumor neo-vasculature or by embolization of antigenic tumor fragments or circulating soluble tumor antigen to other lymphoreticular centers, such as spleen, Peyer's patches, etc., thus initiating a tumor specific immune response.

In our demonstration that syngeneic tumors transplanted to an area devoid of lymphatic drainage will grow progressively despite the eventual development of an active antitumor immune response to the TSTA implies that the immune response directed against such "alymphatic-tumors" is either quantitatively inadequate to prevent continued growth, or is prevented from effectively reaching the tumor. Previous studies using allogeneic tumors grown in areas devoid of lymphatic drainage suggest that failure to reject a tumor isograft is probably related to the tumor-specific immune response being quantitatively ineffective to cause rejection of growing tumors. When 1 × 10^6 viable MCA-A tumor cells are transplanted intradermally into normal allogeneic strain 13 guinea pigs, the tumor grows to only 3 mm. in diameter and is rejected. When transplanted to the allogeneic animal in an area deprived of lymphatic drainage, however, the tumor volume is increased by greater than 500-fold, but still the allogeneic tumor is rejected.[10] The fact that an allogeneic, but not a syngeneic host is capable of rejecting a relatively large MCA-A tumor must be due to the strong histocompatibility antigenic difference between tumor and host. In the syngeneic system, the weaker TSTA, although capable of producing a specific antitumor immune response, are relatively too weak to stimulate an effective response which will reject the tumor once a "critical size" is reached in the alymphatic skin pedicle. The absence of lymphatic drainage from the inoculated area allows the tumor to escape initial host recognition enabling it to attain a "critical size" prior to the development of a systemic antitumor immune response. The failure of tumor to grow in the alymphatic pedicle when isologous tumor is inoculated simultaneously into another intradermal site with intact lymphatic drainage also demonstrates that the effector arc of the immune response remains intact and that lymphatic disruption results primary in a tumor antigen recognition failure.

Crile,[6] in 1965, reported that in a murine tumor system, surgical removal or irradiation of the regional lymph nodes draining an area of tumor allograft implantation reduced the host's immunity to subsequent rechallenge with the same tumor. The incidence of tumor occurrence following rechallenge, the size of the tumor, and the likelihood of distant metastases were all increased in animals subjected to radical regional lymphadenectomy. When simple tumor amputation was performed without removal of the regional nodes, resistance to rechallenge was greater. Attempts to extend these findings to syngeneic, recent origin tumor systems, however, have for the most part been less successful.[1,12,20]

TABLE 1. *Demonstration that the Efferent Arc of the Immune Response Remains Intact in the "Pedicle Model".*

Number MCA-A Tumor Cells	Route of Tumor Inoculation	Number of Animals Growing Pedicle-Tumors
1 × 10^6	I.D. in "Alymphatic Pedicle"	3/3*
1 × 10^6	I.D. in "Alymphatic Pedicle" + I.D. in Normal Skin	0/3

Growth of 1 × 10^6 MCA-A tumor cells was prevented in alymphatic skin pedicles by concurrent intradermal inoculation of MCA-A tumor in intact skin of the contralateral flank.

* $\frac{\text{Number with tumor}}{\text{Number inoculated}}$

Bard, Hammond, and Pilch[1] using a recent transplant generation of a syngeneic carcinogen-induced tumor in inbred mice, showed that adoptive transfer of tumor immunity was successful using regional lymph node cells although surgical removal of these nodes did not significantly alter the host response to a growing tumor or to a tumor inoculation either distal to the lymphadenectomy site or in the contralateral limb. From these studies they concluded that if the regional lymph nodes were important as a site of tumor antigen processing, this function must have been completed prior to the time of lymphadenectomy. No conclusion could be drawn concerning the likelihood of sensitization to tumor-specific transplantation via other lymphoreticular centers. In separate experiments,[2] they have shown that while splenectomy had no effect on the growth of a primary tumor transplant, when the spleen was removed from animals immunized by amputation of a tumor-bearing limb, the immune response to a subsequent tumor cell inoculum was significantly altered.

Hammond and Rolley,[12] using a different syngeneic mouse sarcoma of demonstrable immunogenicity, were unable to demonstrate a significant difference in the incidence of local recurrence or distant metastases in animals with removed vs. retained regional nodes. More recently, using a less immunogenic syngeneic murine

TABLE 2. *Demonstration that Concomitant Tumor Immunity Exists in Animals Bearing Left Flank Pedicle Tumors by the Failure of 1 × 10^6 MCA-A Tumor Cells to Grow in "New" Right Flank Alymphatic Skin Pedicles.*

	No. MCA-A Tumor Cells in Left Flank "Alymphatic Pedicle"	No. Animals Growing Left Flank Pedicle-Tumors	No. MCA-A Tumor Cells in Right Flank "Alymphatic Pedicle"	No. Animals Growing Right Flank Pedicle-Tumors
Bilateral "Alymphatic Skin Pedicles"	1 × 10^6	3/3	1 × 10^6	0/3
Unilateral "Alymphatic Skin Pedicles"	—	—	1 × 10^6	3/3 (Controls)

tumor, Fisher and Fisher[8] have suggested that in the absence of regional lymph nodes a progressively growing tumor is less likely to immunize the host animal. The decrease in immunity following lymphadenectomy was also apparent following amputation of the sensitizing tumor. These findings also suggest that the regional nodes may serve an important role in the initial sensitization to TSTA.

Our model extends each of these studies by demonstrating that total afferent lymphatic interruption prevents source capable of preventing tumor growth. The lack of a functional afferent lymphatic system for delivery of antigen or specifically stimulated small lymphocytes to the regional nodes renders an area an "immunologically privileged site" and these experiments represent the first time such a site has been used to study the induction and progression of syngeneic tumors. Tumors, unlike skin allografts in a "privileged site"[3] will not persist indefinitely without producing an immune response. Both tumor allografts and isografts on alymphatic skin pedicles sensitize the host (by day 20), but only in the allogeneic system is the immune response adequate to cause tumor rejection.

An immune response directed against TSTA and detected in a host bearing a progressively growing tumor is referred to as concomitant immunity. The observation that animals bearing growing pedicle-tumors were resistant to subsequent transplants of the same tumor in a second alymphatic skin pedicle is consistent with this principle and further emphasizes that once immunity to TSTA develops lymphatic interruption plays no part in the initiation or prevention of tumor growth. When tumor antigens are first presented to the host, however, the regional lymphatics are critical in the early development of tumor-specific immunity.

Theoretical speculations based upon this animal model are intriguing. Is it possible that in a clinical situation, a certain anatomic area can spontaneously be converted into an "immunologically privileged site" where an effective immune surveillance system is no longer competent? In such a situation can a somatic cell mutation become autonomous and clones of malignantly transformed cells grow unchecked by the normal apparatus for control of such aberrant growth? Is it conceivable that somehow an isolated portion of, say, the urinary bladder or colon can become an "immunologically privileged site" by interruption of its afferent lymphatic supply allowing normally ineffective carcinogens to escape host recognition and promote tumor growth? While no dogmatic statements can be made, further application of this concept is being applied to other organ systems in an attempt to define the role of "immunologically privileged sites" in tumor growth.

Summary

The relationship of the regional lymphatics to the immunologic response to cancer was studied in inbred guinea pigs. Skin pedicles devoid of their afferent lymphatic drainage prevented early recognition of tumor-specific antigens. An inoculum of syngeneic tumor cells, although insufficient to produce a progressive tumor when injected into intact skin, resulted in a large lethal tumor when injected into alymphatic skin pedicles despite the eventual development of an active anti-tumor immune response.

From these studies we conclude that the afferent lymphatics and regional lymph nodes, although important for early host recognition of tumor-specific transplantation antigens, are not necessary for the eventual development of tumor-specific immunity. Therefore, removal of the local lymphatics, once a tumor has reached a clinically detectable size, should not adversely affect the host's ability to mount an immune response to the tumor since systemic tumor-specific sensitization has already occurred.

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A New Sign of Favorable Prognosis in Mammary Cancer:

Hyperplastic Reactive Lymph Nodes in the Apex of the Axilla

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New York City*

IN EXPLORING the prognostic significance of palpable axillary lymph nodes in patients with mammary cancer, Cutler and associates[2] disclosed that the assessment by the clinician was prognostically significant regardless of the report by the pathologist. The following findings were of particular interest (Table 1): Among patients with no axillary metastases, those with palpable nodes in which metastases were not suspected (group B) had a higher survival rate than either those with nodes in which metastases were suspected (group E) or those with no palpable nodes (group A). Among patients with axillary metastases, those with nodes in which metastases were suspected (groups D and E) had lower survival rates than those without suspicious nodes (groups A and B). The latter finding was expected (suspicious nodes should mean more axillary cancer), but what was not expected was that the prognosis was best of all for patients with node metastases if their nodes were felt but *not* called suspicious (group B). An absence of palpable nodes meant a lower 10-year survival (group A). Hence, whether or not the patients had axillary metastases it meant a better prognosis to have palpable nodes that were not suspected of containing metastases. Also, surprisingly, these findings held regardless of the level (see below) that the metastases had reached in the axilla.

What makes axillary nodes palpable? From Table 1 it is clear that the presence of metastasis is the usual factor. But beyond this, we could discover no information in the literature. Are the palpable nodes in cancer free axillas unusual in any way? Is palpability of nodes in positive axillas related to the number of positive nodes, to their size, or to their location?

The present study then had a two-fold purpose: to investigate the factors determining palpability or nonpalpability of axillary nodes and, in particular, to determine what was special about palpable but nonsuspicious nodes that gave their possessor an unexpectedly good prognosis.

Materials and Methods

At mastectomy, the three axillary levels usually are tagged with metal discs by the responsible surgeon. Level I consists of those nodes lying lateral and inferior to the pectoralis major muscle and thus closest to the breast. Level II nodes lie beneath the pectoralis minor muscle. Level III nodes are medial to the pectoralis minor at the apex of the axilla. Clinically, Level III nodes are recognized by palpating the homolateral infraclavicular area.

During the years 1950, 1951 and 1952, there were 1023 patients with potentially curable mammary cancer who were subjected to radical mastectomy at Memorial Hospital. Rather than study all of the 1023 cases of

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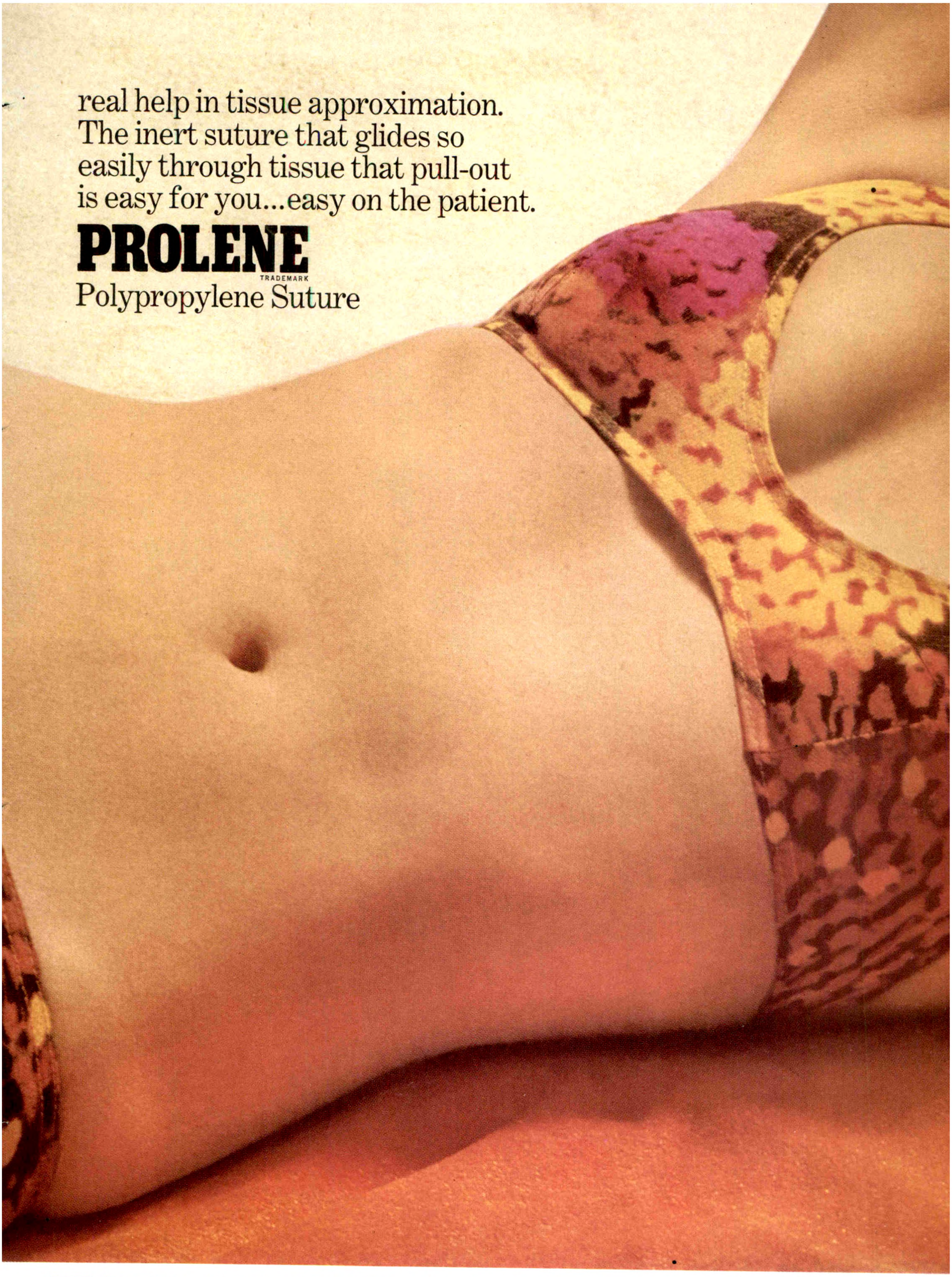

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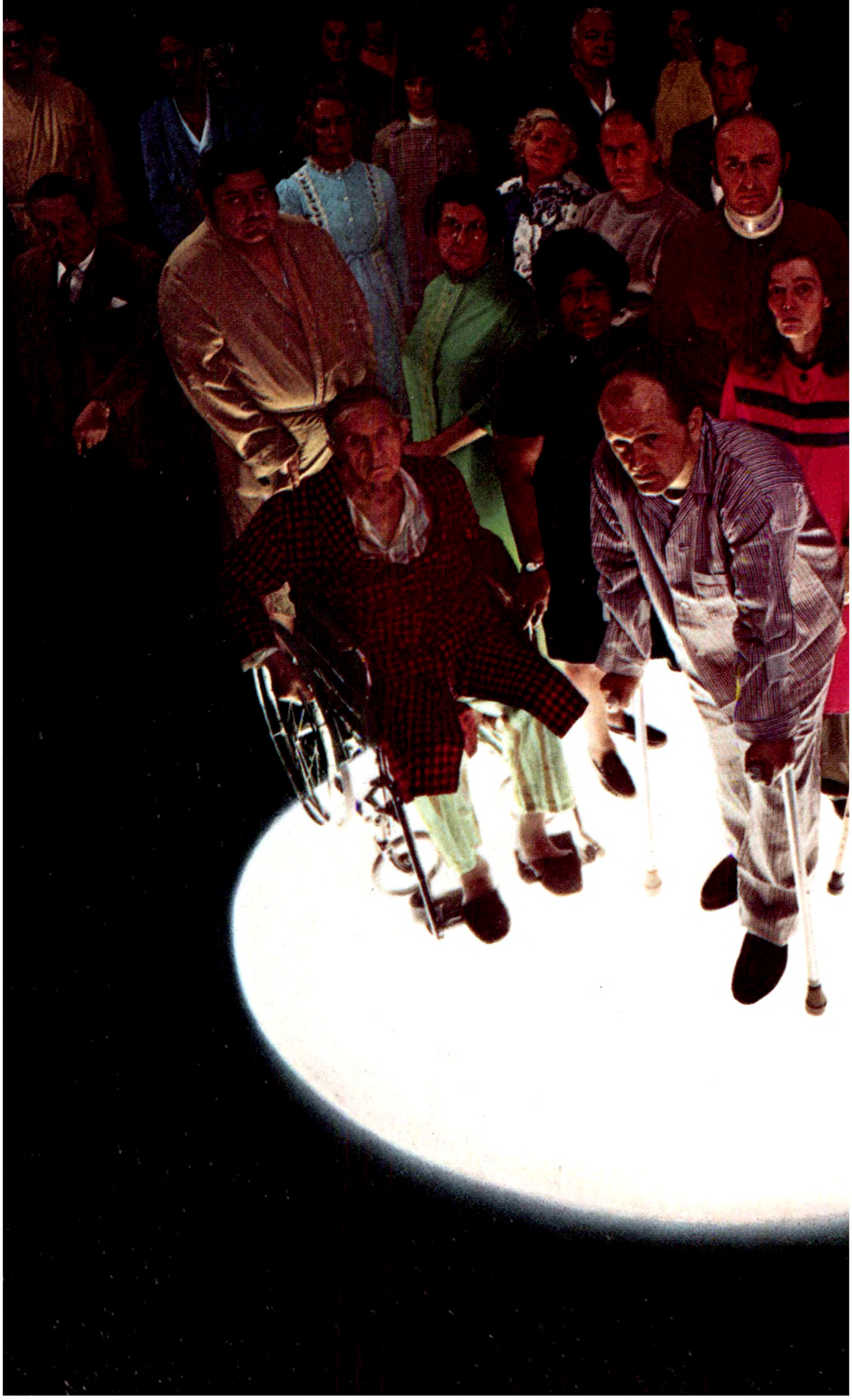

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Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously receiving narcotics have experienced mild withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *other:* tachycardia, soft tissue induration, nodules, cutaneous depression, and ulceration (sloughing) at the injection site, weakness or faintness, chills, moderate transient eosinophilia, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, midlateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist. If naloxone is not available, parenteral administration of the analeptic, methylphenidate (Ritalin®), may be of value if respiratory depression occurs.

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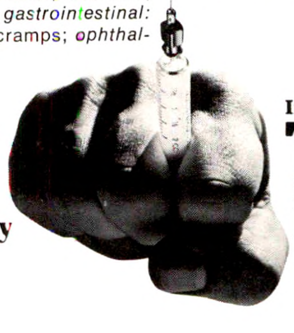

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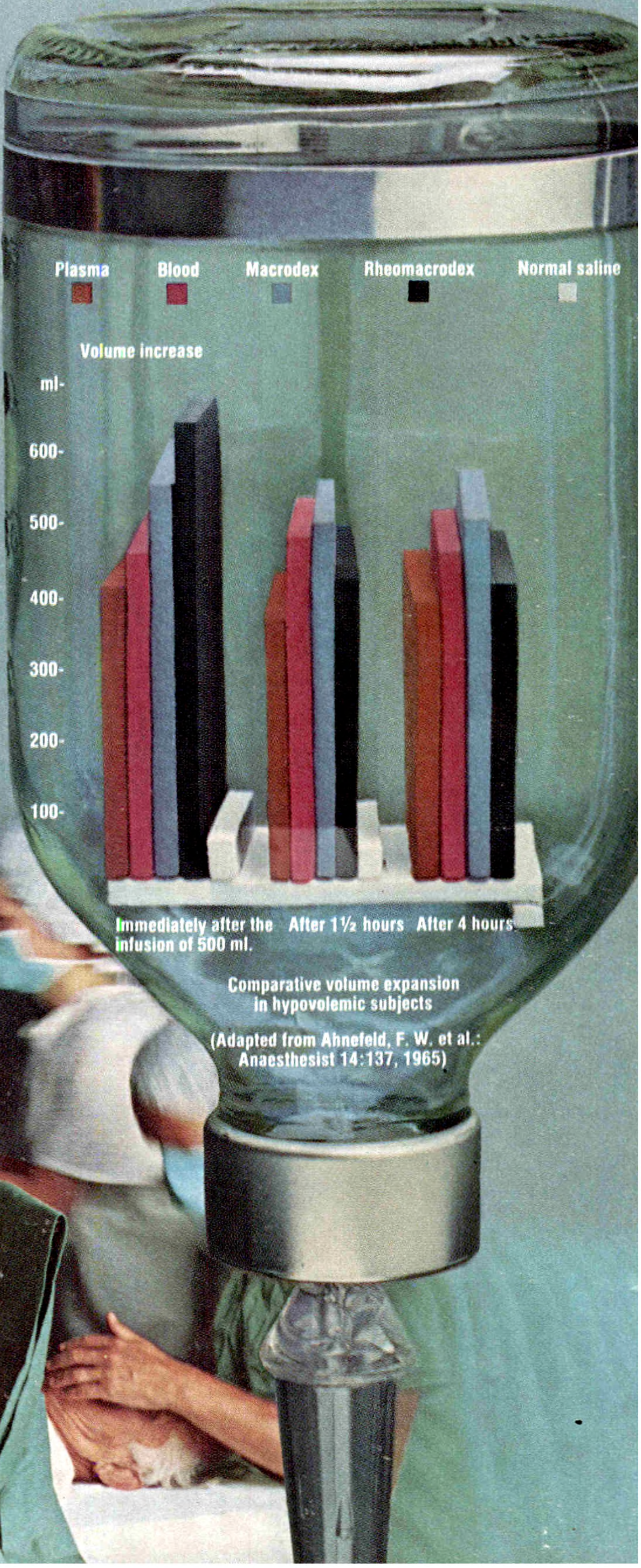

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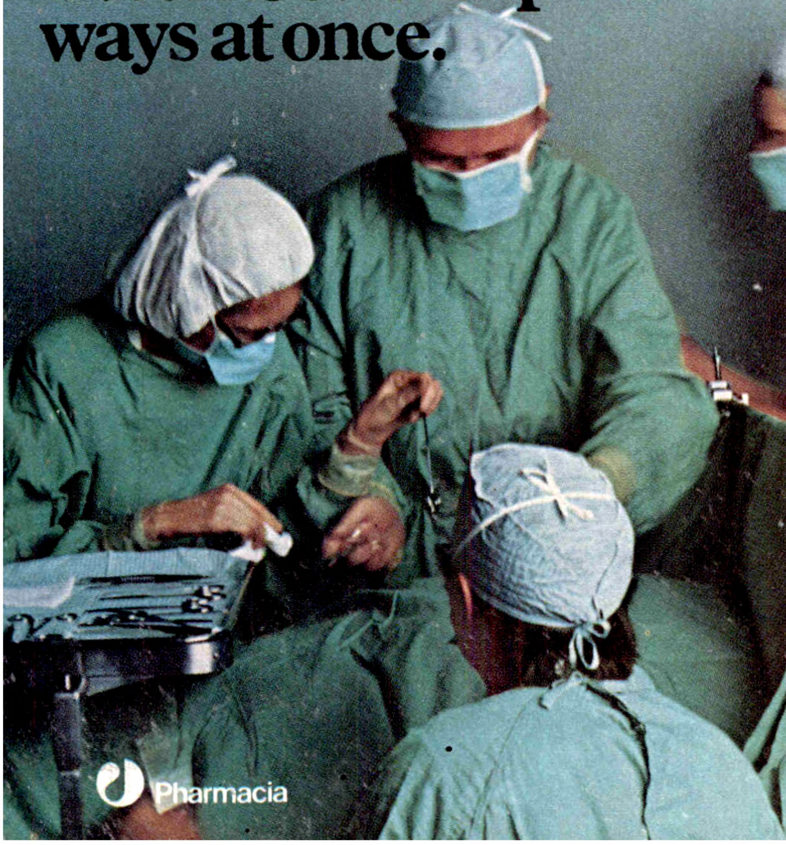

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TABLE 1. *Patient Survival According to Clinical and Microscopic Assessment of the Homolateral Axillary Nodes—Memorial Hospital 1950-52—(From Cutler et al.[2])*

		Pathologists' Report				
		No Metastases		Node Metastases		
Node Group	Definition	No.	10-year Net Survival[*]	No.	10-year Net Survival	Percentage of Cases with Positive Nodes
A	Not palpable	373	77%	266	50%	42
B	Palpable, movable, not stated to be suspicious	42	87%	28	61%	40
D	Palpable, movable, metastasis suspected	15	87%	82	39%	85
			73%			
E	Palpable, fixed, or mobility not specified, metastasis suspected	26	64%	191	24%	88
		456		567		55

[*] Actuarial survival considering only cancer deaths.

Table 1, we chose to work with a smaller group of cases with a representative, balanced distribution of palpability characteristics. Hence a list was prepared of all the cases from the groups with less than 50 cases (B−, B+, D−, E−) plus samples of 20 to 30 cases from the other groups (A−, A+, D+, E+).[*] The samples were chosen at random using the last digit of the case number. One hundred ninety-nine cases were on the final list. Twelve were not studied because of incomplete pathologic material. The most common reason for loss was that the nodes had not been identified by axillary level.

Lymph node measurements were made on Xerox copies of the original slides.[4] Areas containing cancer or other nonlymphoid material were marked on these copies after microscopic review of the matching slides. Only metastases large enough to be seen by the naked eye were counted in tabulations. ("Microscopic" metastases in *resected* nodes have no prognostic significance.[4])

Areas first were measured by planimetry but it proved simpler, faster and more useful to determine the maximum and cross diameters by superimposing a transparent grid (graph paper photographed on a transparent Polaroid(r) film). The grid was such that 20 lines measured 17 mm. Readings were made to the next largest line if an edge fell between two lines. Originally, analysis was done using area values calculated on the assumption that the two diameters were axes of an ellipse. Later, for conceptual reasons and to emphasize that our basic data described palpability of a solid, *volumes* were estimated by assuming the thickness of a node was the same as the smaller of its cross diameters. This brings out the fact that there is three times as much tissue in a node 4 × 3 × 3 mm. as in a thin node 12 × 1 × 1 mm. even though the section areas 4 × 3 and 12 × 1 are the same. Volumes were grouped by choosing division points in a geometric sequence: 1/32 cc., 1/16, 1/8, 1/4, 1/2, 1, 2 cc. plus, since these seemed to give natural groupings of the data. When cancer was present its volume was taken as the estimated fraction of the node replaced (100% in over half the instances). The volume of lymphoid tissue was calculated by subtraction of cancer and other irrelevant material.

Results

A. *Palpability*

When a patient had an axillary node that was at least 2 cc. in volume by our calculation, the clinical examiner always reported the presence of a palpable node. If the largest node was even slightly smaller, there was no correlation between the size of the largest axillary node and palpability (Table 2, 1st column). The probability of the axillary nodes being palpable actually was slightly greater when the largest node was less than 0.25 cc. than when it was between 1 and 2 cc. in volume.

If size of the largest node was important only when the node was as large as 2 cc., perhaps total node volume was the important factor in palpability. This could be

TABLE 2. *Relation of Palpability of Axillary Nodes to the Size and Location of the Largest Node*

	Per Cent Palpable			
		Location of Largest Node		
Volume	All Cases	Level I	Level II	Level III
≥2.00 cc.	100% (16)	100% (13)	100% (3)	—
1.00-1.99	72% (25)	67% (15)	75% (8)	100% (2)
0.50-0.99	78% (41)	74% (23)	75% (12)	100% (6)
0.25-0.49	65% (55)	65% (34)	61% (18)	100% (3)
0.25	76% (50)	65% (26)	85% (20)	100% (4)
All	75% (187)	71% (111)	75% (61)	100% (15)

Numbers of cases in parentheses.

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[*] The letters refer to the "Node Groups" of Table 1; the − and + to the absence and presence, respectively, of metastases on pathologic examination.

TABLE 3. *Relation of Palpability of Axillary Node to Size of Largest Node at Apex of Axilla (Level III) (16 Cases with a Node ≥2 or Larger at any Level Excluded)*

Volume (cc.)	Cases	Palpability
≥0.25	18	100% (18)
0.125–0.24	17	94% (16)
0.125	136	66% (90)
	171	124

determined for all negative and most positive axillas but, excluding the 16 cases with 2 cc. nodes, there was no discernible correlation between total node volume and palpability. Neither did it matter whether the nodes were mostly cancer, mostly lymphoid tissue or mostly fat. Palpability still seemed to be a random property.

Finally, location of nodes was taken into account. Again omitting the 16 patients with nodes 2 cc. or more in size, it made no difference how the nodes were distributed between levels I and II (Table 2). However, it did make a difference how big the nodes were in the apex of the axilla. Patients who had a node at level III at least as large as ¼ cc. were *always* reported to have had palpable nodes. If the largest node at level III was between ⅛ cc. and ¼ cc., 16 patients out of 17 (94%) were reported to have had palpable nodes. However, when the largest node at level III was less than ⅛ cc., only 66% of patients were reported to have had palpable nodes (Table 3).

We see from the above that of the 51 patients with a maximum-sized node of at least 2 cc. at any level (16 cases) or at least ⅛ cc. at level III (35 cases), 50 were reported to have palpable nodes. These 50 accounted for more than one-third of the 140 patients with palpable nodes. No other factor examined was found to increase the likelihood of node palpability. Other hypotheses, such as that obesity might have decreased palpability, were not confirmed. Chart review, like slide review, failed to provide further reasons for palpability or its absence.

TABLE 4. *Relation of the Size of the Largest Level III Node to the Correct Assessment of Axillary Metastases*

Cases					
Cases with Palpable Nodes	146				
Not evaluated for presence of cancer		42			
Cancer suspected		79		52%	
Level III nodes ≤1/8 cc.			17		88%
Other cases			62		42%
Nodes called benign		25		64%	
Level III nodes ≤1/8 cc.			7		71%
Other cases			18		61%
Palpable Nodes not Reported	41				

Accuracy significantly greater with an enlarged node at level III ($X^2 = 8.8$, $p < 0.01$)

An enlarged node at the apex of the axilla meant more than just a high likelihood of node palpability. It also meant that the examiners were much more accurate when they evaluated the axillary nodes as benign or containing cancer (Table 4). Diagnostic accuracy in the overall series, of course, was much greater than that shown in Table 4. The sample described in the table contains *all* false positive and false negative node evaluations but only a small part of the cases in which the clinician's estimate of axillary node status was correct. Estimating the frequency of level III enlargement from the sample, in the full series of Cutler *et al.*[1] the clinical suspicion of cancer would be correct for 100 of 102 patients with enlarged level III nodes and correct for only 173 (83%) of the 209 other patients. For all evaluations, both positive and negative, of *palpable* nodes, the accuracy would be 96% with level III enlargement, 79% without it. (The major problem, of course, in the clinical evaluation of the axilla is that 47% of patients with *no* palpable axillary nodes still have axillary metastases.)

B. *Prognosis*

The second problem we set ourselves was to see what characteristics of the axillary contents might relate to prognosis as well as to palpability. The obvious property that came to mind was the amount of cancer in the lymph nodes. However, we failed to find any correlations between the amount of cancer and either palpability or prognosis. This is not to say that a correlation between amount of cancer and prognosis does not exist, because it almost surely does. Instead, our failure to find a correlation probably arose because the case material was unsuitable. The one objective of pathologic examination of the axilla during the early 1950's was to determine which levels contained cancer. The instructions were that if there were obvious metastases at a level, only the two largest nodes had to be sectioned. There was no attempt to quantitate axillary cancer then, and we cannot compensate for missing data now. This missing in-

TABLE 5. *Net 10-year Survival Related to Level of Axillary Metastases and Amount of Benign Lymph Node Tissue at the Apex of the Axilla*

Highest level at which metastases found	Net Survival		
	<1/32 cc. Benign node	1/32–1/8 cc. Benign node	>1/8 cc. Benign node
None	65% (46)	82% (29)	93% (27)
Level I	63% (17)	100% (3)	83% (6)
Level II	36% (15)	50% (2)	68% (7)
Level III	21% (18)	0% (5)	42% (12)

Number of cases in parenthesis . . . Total: 187

formation probably also accounts for our failure to find any explanation for the different survival of Group D (suspicious but movable nodes) and Group E (nodes suspicious but not called movable).

What was discovered during the attempt to quantitate cancer was that survival was very clearly correlated with the amount of *uninvolved* lymphoid tissue at level III. As Table 5 shows, little uninvolved node tissue at the apex of the axilla meant poor survival, while more meant better survival. When there were "enlarged" nodes at the apex of the axilla and no metastases, the 10-year breast cancer net survival rate was 93% while it dropped to 65% when apical node tissue was at a minimum. When there were metastases in the upper axilla (levels II or III), 10-year survival for the patients who had more than ⅛ cc. of benign node tissue at the apex was twice what it was for patients who had little or none.

Studies were also run on the relationship of uninvolved node tissue at lower levels to survival and no correlation was found.

C. *Microscopic Findings* (Table 6)

Microscopic examination of axillary lymph nodes of all patients was undertaken. One hundred and forty-nine patients had negative lymph nodes at level III, and forty-six patients had metastatic carcinoma in the level III lymph nodes. Of these, 38 patients exhibited macrometastases and eight micrometastases.[4] Of the 149 patients with negative lymph nodes at level III, 121 had sinus histiocytosis and 19 prominent germinal centers. Eighty-five patients, in addition, had marked fatty infiltration of the level III axillary lymph nodes. Forty-three patients with histologically negative lymph nodes had either tiny or unremarkable lymph nodes in the axillae.

Of the 38 patients with macrometastases in level III lymph nodes, 28 demonstrated that the metastatic carcinoma either involved the lymph node capsule or extension into perinodal adipose tissue. In eight instances the metastatic lymph node involvement was total with no lymphoid tissue retained. Sinus histiocytosis and prominent germinal centers were present in 13 and 9 instances, respectively.

Micrometastases in level III lymph nodes were found in eight instances. Sinus histiocytosis in five, and prominent germinal centers in one instance were found in the lymph nodes of this group of patients.

TABLE 6. *Correlation of Palpatory and Histologic Findings in Level III Axillary Lymph Nodes*

	Clinically Palpable and Suspicious	Clinically Palpable and not Suspicious
Total Number of cases	38	34
Negative nodes	25 (65.8%)	29 (85%)
Positive nodes		
Macro	11	4
	13 (34.2%)	5 (15%)
Micro	2	1
Sinus Histiocytosis	24	25
Prominent germinal centers	1	9
Fatty infiltration of nodes	7	13

Discussion

Our quantitative studies of axillary nodes brought out two facts. Firstly, nodes were most likely to be palpated and assessed accurately when apical axillary nodes were enlarged. Secondly, prognosis was better when there was increased *benign* lymphoid tissue in the same apical nodes. Together, these facts help explain the survival paradoxes. For the patients with no axillary metastases, if no axillary nodes were palpated, there was no case in our sample with an enlarged level III node. If nodes were palpated but called suspicious, there rarely (2/38) was an enlarged level III node. Hence enlarged level III nodes were found almost entirely in patients whose nodes had been palpated but not called suspicious (Group B). Since enlargement of benign level III nodes meant a 93% ten-year survival rate, it is not surprising that the B− group had the best survival experience.

A similar trend was seen when metastases were present. Patients with the most benign lymphoid tissue in apical nodes were concentrated in the B+ group whether or not the apical nodes also contained cancer. Since the correlation between benign apical tissue and good prognosis held even with node metastases, it is logical that the B group with palpable but nonsuspicious axillary nodes would have the best prognosis.

Microscopic examination of the enlarged apical nodes indicated two reasons for the prognostic importance of the apical nodes. Usually apical nodes are too small to feel. When they are enlarged it is either because there is cancer present or because the nodes are reactive. If cancer is present, it is physically close to the general circulation, and if the cancer nodule is large enough to be palpable, it almost always will be extending through the node capsule because the nodes are so small. Such extension is a mark of particularly poor prognosis.[3]

When nodes are enlarged without the presence of cancer they are by definition reactive. Usually this reactivity was manifested as sinus histiocytosis, less often as germinal center hyperplasia. Our data suggest that, other prognostic factors being equal, reactivity of these particular nodes is an especially good portent of better prognosis.[1]

We conclude that the clinical evaluation of axillary status contributed information beyond that found in the pathologist's study because the presence of palpable, nonsuspicious nodes often meant that there was increased benign lymphoid tissue in the apex of the axilla. The patient's chances of survival were better with increased lymphoid tissue in this region. With axillary palpation the clinician may have measured host resistance as well as progression of the patient's cancer.

Summary

Enlargement of nodes in the apex of the axilla meant more accurate clinical evaluation of the axillary status by the clinician. If the enlarged apical nodes were not replaced with cancer, prognosis was better for any degree of axillary metastasis than if the nodes were tiny or absent. These two facts explain much of the previously noted paradoxical findings that suspicious axillary nodes meant a poor prognosis although no metastases were found therein, while clinically "benign" nodes meant a good prognosis although metastases actually were present.

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Disappearance of Disseminated Pancreatic Carcinoma with Combined Chemotherapy

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PANCREATIC CARCINOMA is an occult malignancy that is typically diagnosed late in the natural course of the disease when dissemination has often developed and the 5-year survival rate is consequently low (less than 5%).[5] Systemic therapy using radiation alone or in combination with specific chemotherapy, 5-fluorouracil (5-FU), has been only partially successful in prolonging survival.[1,2] A combination of chemotherapeutic agents, 5-FU and 1,3-bis(2-chlorethyl)-1-nitrosourea (BCNU)[3] was employed in a patient with disseminated abdominal and pelvic pancreatic carcinoma. A "second look" laparotomy for small bowel volvulus disclosed the complete disappearance of previously proven peritoneal and omental tumor seeding.

Case Report

C. C., (PBBH #10-77-93), A 42-year-old man entered the hospital in January 1969 with progressive diarrhea and weight loss. He had had gray, oily stools, which contained both neutral and split fat products and partially digested meat fibers. An upper GI series revealed an impression on the duodenal loop, suggesting a mass in the head of the pancreas. A secretin test produced a normal volume of secretions but no bicarbonate or amylase was present in the duodenum. An arteriogram revealed no evidence of tumor. Cytology of pancreatic secretions did not reveal tumor and the patient underwent laparotomy. He underwent total pancreatectomy and splenectomy with hemigastrectomy, vagotomy and duodenectomy. Microscopic examination of the specimen revealed a moderately well differentiated ductal adenocarcinoma arising in the head of the pancreas with extension into duodenal muscularis, ampulla and into two contiguous lymph nodes. In addition there was metastatic carcinoma in one of five peripancreatic nodes. Adenocarcinoma was also found in the body of the pancreas but the tail of the pancreas had only chronic active pancreatitis with fibrosis. Postoperatively the patient responded well and subsequently was maintained on Viokase and insulin replacement therapy. He returned to work and his weight stabilized at 130 lbs, 30 lbs. below the preoperative level.

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In July 1970 he noted a nagging right upper quadrant discomfort, which was non-incapacitating but progressive in intensity. On examination, in September 1970, he had a palpable right upper quadrant mass and a firm mass on rectal examination. Exploratory laparotomy for palliative considerations was undertaken, at which time diffuse carcinomatosis was observed with a large mass in the pouch of Douglas. The liver itself was free of gross tumor. There was minimal ascites. Biopsy of a peritoneal implant was consistent with adenocarcinoma of pancreatic origin. Postoperatively the patient was begun on a combined chemotherapeutic program using 5-FU, 7 mg./Kg. and BCNU, 35 mg./M^2. Each drug was given daily by the intravenous route for 5 days at 6–8 week intervals. The patient experienced a gradual regression over the next 2 months of the pain syndrome and in addition, there was marked regression of the rectal mass as well as the right upper quadrant mass. With two further courses of therapy, continued regression of symptomatology as well as palpable lesions was observed.

In April 1971, 21 months after the initial operation and 7 months after the initiation of chemotherapy, the patient developed an acute episode of overwhelming abdominal pain and on examination had signs of an acute abdomen with rigidity and peritoneal irritation. An emergency exploratory laparotomy revealed an apparent volvulus of the small bowel with overt necrosis of jejunum and ileum. An extensive resection of the bowel with a jejuno-ileal anastomosis was established. All but 3 feet of jejunum and 2 feet of ileum were removed. No colon was removed. There was no evidence of tumor grossly and extensive pathologic evaluation revealed only infarction of the 350 cm. of resected small intestine with multiple thrombi in the veins. An analysis of mesenteric lymph nodes, 55 in number, revealed no evidence of tumor. Postoperatively the patient has responded well to medium chain triglycerides, Vivonex and Viokase and has gained 10 lbs. in weight. He has continued to receive courses of combined 5-FU and BCNU chemotherapy which are administered every 8–10

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weeks. Five months following small bowel resection, his bowel function is adequate with the passage of six to eight soft stools daily. It is now 12 months since the abdominal exploration at which time extensive tumor spread was found intraperitioneally. There is no evidence of recurrent tumor to date, and he has resumed his usual occupation. The patient is still well without evidence of recurrence, Nov. 1972, 26 months following onset of treatment with the above chemotherapy combination. He has continued to receive chemotherapy at set intervals of time.

Discussion

Surgical, radiotherapeutic and chemotherapeutic programs employed singly or in combination in the treatment of pancreatic ductal carcinoma have been uniformly unrewarding. Definitive surgical treatment has been abandoned by some[2] in view of the fact that disseminated carcinomatosis may develop within weeks of extensive radical resection (Whipple procedure) for what may appear to be well-localized cancer at the time of operation. Brooks[4] and others have recently pointed out the inadequacy of the Whipple procedure (removal of the pancreatic head only) for carcinoma of the pancreatic head and have suggested that the more complete procedure (total pancreatectomy) be performed instead. Such a procedure was performed as the initial operation in the present case.

The use of chemotherapy for disseminated carcinoma of the pancreas has been disappointing. Reitemeir, Moertel and Hahn[5] suggested the use of a combination of 5-FU and BCNU for pancreatic carcinoma. They noted objective responses in two of three patients, defined as the reduction in lesion size of more than 50% at 8 weeks of therapy. Details of the cases were not available. In addition, responses to either 5-FU or BCNU used alone were rare. An earlier report by Allaire *et al.*[1] noted objective responses in two of three patients treated with 5-FU alone and three of four patients treated with combined 5-FU and X-ray therapy but the median survival observed was less than 6 months.

The rationale of combined chemotherapy involves an attempt to utilize agents which are known to be effective singly in order to obtain a synergistic response. Combined agents which effect cellular function at different levels or in different phases of cellular growth may potentiate the therapeutic effect of the agent and by modifying doses and time of application a reduction in toxicity may be achieved.

5-FU is an antimetabolite and the antitumor effect is a consequence of a block in the conversion of deoxyuridine monophosphate to thymidine monophosphate. 5-FU, therefore, inhibits DNA synthesis and requires metabolically active and duplicating cells in order for an effect to be observed. BCNU is an alkylating agent primarily, although antimetabolite effects have been suggested. Alkylating agents are effective in cellular resting phases as the mechanism of action involves disruption of the DNA strands. Hence, the use of these agents in combination is ideal for the potentiation of the antitumor effect of each drug.

The response of our patient is admittedly anecdotal and perhaps only transient but the dramatic response of this neoplastic process, which is generally associated with rapid deterioration, emphasizes the need for further investigation of these combined agents for use in surgical treatment of pancreatic carcinoma. This patient illustrates the variable biologic process of pancreatic tumor growth and points to the possibility that chemotherapy can effectively reduce a tumor mass, and may prolong survival in some patients.

Acknowledgment

The major contribution of Dr. Philip Snodgrass to this patient's care is herein recorded.

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Familial Malignant Melanoma

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MALIGNANT MELANOMA in Queensland has an annual incidence of 16.4 per 100,000 population[7] and it has been calculated[19] that the risk to the average person who survives to 80 years of age or over in this State amounts to approximately one in fifty. It is therefore to be expected that in any large study of this disorder melanoma will have occurred as a chance association in more than one individual in some families. Whether the association is more than fortuitous will depend on a close study of those families in which more than one instance has occurred.

We present some findings from a study of 42 pedigrees taken from the records of the Queensland Melanoma Project. This study was undertaken to determine whether there is an hereditary element in the etiology of the condition, and if so, whether a discernible pattern of inheritance can be detected, and whether familial malignant melanoma behaves differently and should be regarded as a separate form of melanoma.

Description of the Study

From the records of the Queensland Melanoma Project details were extracted from all cases in which a family history of malignant melanoma, proven or suspected, had been obtained. The individuals concerned, or, in the event of their death, a surviving relative, were then contacted. Wherever possible, this was done by personal interview, but in a few instances correspondence, followed by a long distance telephone call to the family member concerned, was regarded as sufficiently informative to obviate a journey, which in Queensland might represent more than 2,000 miles of travelling. Even so, several journeys of this length were made in search of data. Interviewing was carried out by one of the authors, on some occasions following an initial approach by a trained member of the Genetics Department of the Queensland Institute of Medical Research. A group of control patients, matched for age and sex, was assembled from several orthopedic and general medical patients and hospital employees. They were interviewed similarly to the patients with melanoma. Sixty-six clinical records in which the occurrence of malignant melanoma in a relative had been noted were obtained from the 1676 documented records of the Queensland Melanoma Project. As explained in published descriptions of the Project[3,6] the complete case histories were not obtained from every case recorded in the files and therefore these 66 were culled from a total of 473 in which the family history had been recorded. In 16 of these families, the case of another member of the same family had been documented (double and even treble ascertainment). Thus there were 50 families in the records of the Project in which more than one case of malignant melanoma had been recorded. In five of these families proof that the second instance was malignant melanoma could not be established. Four were probably benign or questionably malignant active junctional naevi and the fifth was a case of misreporting; the lesion proved to be carcinoma of the lung. Two of the families could not be contacted. In one family only, due to an uncooperative propositus which resulted from a tactless initial approach, it was impossible to obtain a satisfactory record of the family tree. Thus a total of 42 families was studied in detail. Family trees were investigated and records were compared with those of the Melanoma Project for age, sex and matched controls. Specific details regarding these items were recorded: age at onset, sex, number of first degree relatives, degree of relationship between the propositus and the other affected members, incidence and

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nature of malignant lesions other than melanoma, the site of the melanoma, its size, histological classification, state of the regional nodes, mortality, the patient's skin color, hair color, eye color, skin texture, resistance to sunburn, the previous exposure of the area of the lesion to sunlight, the presence of other suspicious naevi, the occupational and recreational exposure to sunlight, the age at menarche and menopause in women and the number of children born to them, the places of residence of the propositi, and lastly, the country of origin of their parents and grandparents. The following is a record and discussion, item by item, of the results of this comparison.

Familial Pattern

We could discern no pattern of incidence which resembled the action of a single major gene in these families. None of the pedigrees suggested that either recessive or sex-linked alleles or dominant alleles with or without incomplete penetrance were involved. In particular there was no kindred approaching in similarity the appearance of the large family as reported by Anderson, Smith and McBride.[1] Representative families are shown in Figure 1. No instance of consanguinity was detected among the parents of any case.

In a previous study,[19] the incidence of second instances of malignant melanoma in relatives of index patients was higher than among the general population. In these families in which more than one instance of melanoma occurred there was a still higher than expected incidence of third cases. Seven examples were recorded in which three instances had occurred among first degree relatives in the one family. This incidence is more than would have been expected among the 331 first degree relatives in these families, excluding the propositus and the second affected case.

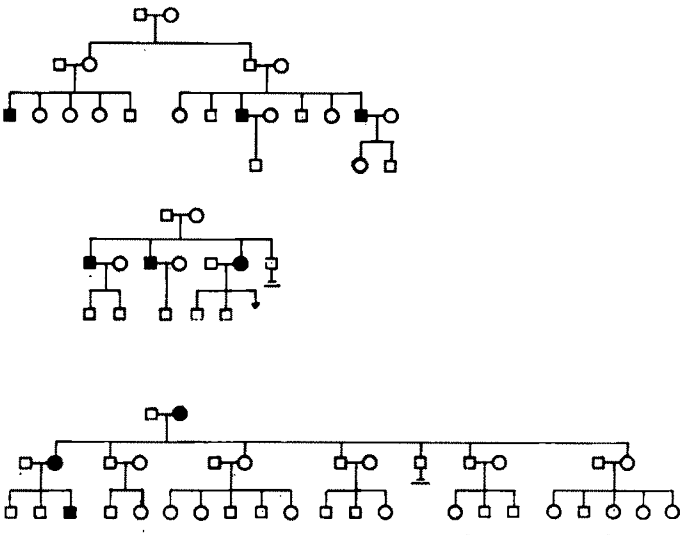

FIG. 1. Three pedigrees showing the distribution of malignant melanoma cases.

The calculation is as follows: In the previous study the incidence of melanoma among first degree relatives of patients with malignant melanoma was calculated to be 0.012 compared with an expectation of 0.0072 for a group of the general Queensland population of the same age and sex distribution. This would lead to an expectation of just less than four instances among the remaining members of the families concerned. The figures are small, but they suggest that when a second instance occurs in a family, the risk to further members may be raised still further. Since the expected figure was based (as will be shown) on an older age group of relatives, it is an over-estimate and the increase in liability may be twice the previous raised value. This estimate may indicate the action of a polygenic system, which we would suggest is the probable cause of the familial pattern shown here.

It might be argued with reason that the system which is demonstrated in these families may be due to the effect of a common environment within the family exerting a carcinogenetic influence. Our data indicate that in many families collateral lines are affected, which reduce considerably the possibility that environmental and cultural influences are entirely responsible, yet in some instances a suspicion remains that a common environment has played a part in the genesis of the condition. It has been established[7,10,11] that exposure to sunlight is associated with an increased incidence of malignant melanoma among people of Caucasian stock. The records of one of the families included in this series contains two cases. A brother and a sister developed malignant melanoma at an early age; their childhood had been spent on lighthouse islands off the Queensland tropical coast never south of the Tropic of Capricorn, during which period they would have experienced intense exposure to sunlight. We were unable to demonstrate that the familial patients of melanoma had any greater occupational or recreational exposure to sunlight than a matched group of control patients and feel that this factor is unlikely to be the explanation for the familial accumulation of malignant melanomata.

In order to study the hypothesis that one sex might have a greater influence on the transmission of the tendency to acquire melanoma from one generation to another, that is, that there may be maternal or perhaps cytoplasmic influences at work, a tabulation was made of those cases in which a male parent or a female parent had been interposed in the line of descent from one instance to another, or in which a male or female affected parent had had an affected child or children. In only 27 of our families had there been apparent transmission across generations in such a way that such a parent could be identified. In 17 cases the parent responsible was female and in ten it was a male. The excess of transmission in female lines is interesting, but could have occurred by chance once in six trials, assuming no effect of parental sex, so it is best to accept that the null hypothesis of equally effective transmission by either parent holds, but that the possibility of a maternal influence on transmission remains. The 15 families described by Turkington[18] do not show a preponderance of transmission in female lines.

Our conclusion regarding this aspect of the study is that there is a true, genetically determined tendency to develop melanoma in at least some and probably a majority of these families, and that this tendency would appear to be of a polygenic nature. In addition, it is probable that the effects of a common environment within families are responsible for some of the familial tendency demonstrated. There is no suggestion that a single abnormal allele is responsible for these familial cases.

Comparison of the Groups

1. *Number of First Degree Relatives:*

It might reasonably be thought that the familial group might comprise a subset of the melanoma records characterized by large family size, thus permitting a greater chance for second instances of melanoma to occur among them. This is not so. Though there was a slightly higher family size among the propositi of the families with a history of melanoma, the difference was not significant. The average number of first degree relatives of the 42 propositi of the melanoma families was 9.275 ± 3.99, and of those of 100 consecutive cases from the Queensland Melanoma Projects records was 8.270 ± 3.85 ($t = 1.479$, $0.2 > p > 0.1$). Thus mere size of the families does not account for the accumulation of melanomata among them. It is probable nevertheless, that chance occurrence among near relatives has caused several families, in which there is in fact no greater tendency to develop malignant melanoma than exists among normals, to be included in this series. Inclusion of these families would dilute the statistical effect of differences between the true familial cases and the ordinary melanoma cases if such differences exist.

2. *Age:*

The average age at onset of the familial group and of the patients with general melanoma did not differ appreciably, that of the 58 documented familial instances being 41.83 ± 16.74 years and of the melanoma instances in total being 42.37 ± 16.82 years ($d = 0.777$, $0.5 > p > 0.4$). However there were very significantly more young patients in the familial group, for 15 of the 58 familial patients were below 30 years of age, although only 195 of 1516 documented cases in the general melanoma records were in this category ($x^2 = 8.16$, $0.01 > p > 0.001$). This conforms with the observations of previous authors.[1]

3. *Multiple Primary Melanomata:*

No less than eight of the 58 patients had had multiple primary lesions, more than one in seven, and five of these had had three or more lesions. This is in striking contrast to the rarity of this finding among patients with melanoma in general, only 49 such cases were recorded among the 1458 cases in whom this item had been specifically recorded. This confirms previous observations also.[1,5,12,18]

These two findings—multiple primary lesions and early age at onset—may be taken as further evidence in favour of our thesis of polygenic determination, of the tendency to develop malignant melanoma. It is known that the incidence of a polygenic trait is higher among the close relatives of severely affected patients than of mild instances[4] and a young person with multiple primary lesions may reasonably be claimed to be more severely affected with a tendency to this disease than a patient who develops a single lesion late in life.

4. *Site and Nature of the Lesion:*

We were unable to demonstrate that there was any preferred site for the melanomata occurring in the famil-

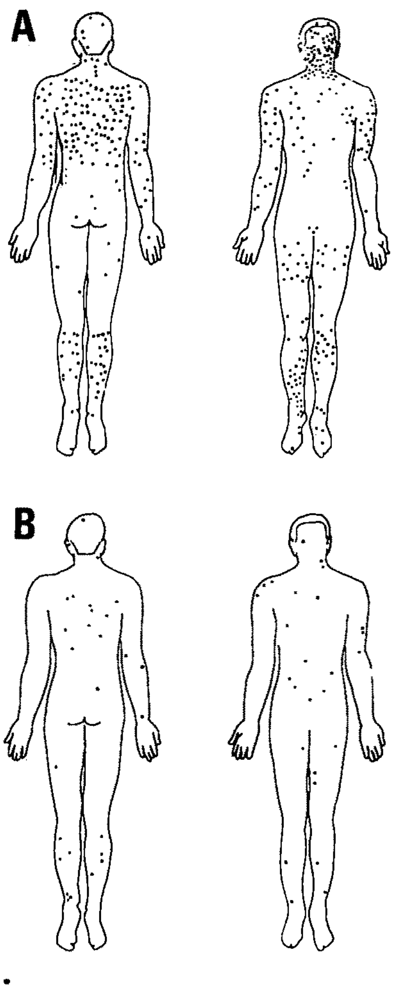

FIG. 2. Comparison of sites of origin of sporadic and familial melanomata. A. Sites recorded for 400 cases recorded from the Queensland Melanoma Project records. B. Sites recorded for 55 familial cases.

ial instances. There does appear to be a distinct tendency for the melanomata in the familial patients to occur at random over the skin surface as distinct from the sporadic instances in which there is a distinct clustering in certain areas such as the face, back, shoulders and legs. This is best demonstrated by reference to Figure 2 in which there is a graphic representation of the sites of the lesions in four hundred documented cases and in the fifty-five familial cases in which the sites of the lesions had been accurately recorded. In particular the absence of facial lesions in the familial series is obvious, and is statistically significant at the 0.05 level. The macroscopic and histologic features of the lesions from the patients with positive family histories were not found to differ from those found in the sporadically occurring majority.

5. *Racial Origin:*

Table 1 shows the country of origin of the grandparents of the propositi of the melanoma families and of those of the age—and sex-matched controls. It will be noted that there is an excess of people of Celtic and Northern European ancestry and a deficiency of Eastern European and other ancestry among them. (The records of the Queensland Melanoma Project contain no example of the disease among the Australian aboriginal stock either of pure descent or mixed.) These figures are significant at the 0.05 level of significance. It does appear that people of Scottish, Irish, and Welsh descent and to a lesser extent, of Northern European ancestry, are particularly prone to develop cutaneous malignant melanoma in Queensland.

6. *Reaction of the Skin to Ultraviolet Light.*

Table 2 shows the comparison between the familial, the control and the general melanoma groups in this regard. Though in the control group those who suntanned easily were in the majority, while the reverse was the case in the groups with melanoma, the distinction was a finely balanced one, and statistically nonsignificant. There is no obvious departure from the general population pattern in regard to this trait.

TABLE 1. *A Comparison of the Ancestry of the Familial Cases with that of Age and Sex-matched controls*

	Control Sample	Propositi of Familial Cases
Grandparents		
English	19	18
Scottish	7	16
Irish	8	10
Welsh	0	1
Northern European	5	12
Southern European	0	0
Eastern European	2	0
Australian & Unknown	38	25
Other	5	2
	Controls	Propositi
Scottish, Irish, Welsh,	15	27
All Other	69	57
$x^2 = 4.57$	$0.05 > p > 0.02$	

TABLE 2. *A comparison of the Reaction to Exposure to Sunlight among the Groups Studied*

	Control Subjects	Familial Group	All Cases of Melanoma
Tan easily	21	17	201
Sunburn easily	18	23	219
Undecided	3	2	45

$x^2 = 1.2768$

7. *The Influence of Age at Menarche and Parity in Female Patients.*

There were no significant differences found in this regard. Table 3 shows the findings. It will be noted that the female propositi of the melanoma families had an earlier menarche and more children than either the control group or the melanoma group, but that the difference does not reach levels of significance. Only 240 completely documented female patients with melanoma from the Brisbane Teaching Hospitals were specifically questioned regarding menarche and number of children, hence the comparison is with them.

8. *Factors Which Showed No Suggestion of Correlation with Familial Melanoma.*

The findings of hair color, eye color and skin texture had the same distribution among the propositi and the controls and it cannot be established that they were indicative of any inborn tendency to melanoma. As already noted, occupational exposure to sunlight and recreational exposure to sunlight and in addition the presence of any solar keratoses now and in the past showed the same distribution among controls and propositi. It would appear that differences in environmental exposure to sunlight, though obviously connected in some way with the increased likelihood of developing melanoma in Queensland do not account for the familial aggregation of melanoma cases under discussion. There was no correlation between the size of the melanoma, its histologic classification or the state of the lymph nodes and familial melanoma, nor was there any relationship to mortality from the disease.

9. A curious finding, which may be an artifact owing to the attention drawn to malignancies in these families, or which may have a real basis, was the high incidence of malignancies of all types among the first degree relatives. Among a total of 441 first degree relatives with melanoma in these families, 33 cases of malignant disease were recorded. This was more striking when one

compared deaths from malignant diseases as a proportion of all deaths among first degree relatives in these families. One third of all the deaths in women and one fifth of all the deaths in men, excluding those due to melanoma, had been due to malignant disease. This was higher than the proportion of deaths to be expected from this cause in Queensland, significantly so for women. The actual numbers concerned are listed in Table 4. The expected numbers were calculated from data in the Commonwealth Year Book, 1969, weighting the results according to the age at death of the relatives.

These findings can not be checked adequately with the data here presented, but they suggests that the occurrence of two or more malignant melanoma cases in the one family may indicate a general inborn liability to malignant transformation of tissues in these families, or in other words, that "cancer families" do in fact exist. A similar conclusion was reached in the earlier study of Lynch and Krush.[12]

Discussion

It is apparent from the literature concerning familial cases of malignant melanoma that in most of the published reports it was the curiosity value of the cases that prompted their appearance in the literature. Such appear to have been the cases of Cawley,[5] Andrews,[2] Katzenellenbogan and Sandbank,[9] Salamon, Schnyder and Storch[15] and others.

A notable advance was the excellent paper by Anderson, Smith, and McBride,[1] who described a total of 22 families, including one in which there were no less than 15 cases of malignant melanoma in several generations. The concentration of malignant melanomata in this, their Kindred No. 1, gave the appearance of a single allele segregating in the family with dominant expression in the heterozygote, and occasional lack of penetrance. Nevertheless, Edwards[8] has warned of the simulation of Mendelism when more than a single allele is involved, and a close examination of this kindred will show that it could equally well be explained on the basis of a rare concurrence of a series of factors influencing the development of malignant melanoma with a greatest concentration in the genome of II$_1$ and II$_2$, parents of III$_1$–III$_5$. From there the frequency of malignant melanoma becomes less with each step outwards in kinship from this central focus, as one might expect with the dilution effect of polygenic inheritance. Alternatively, one must recollect that there is at least one disorder inherited in strict Mendelian recessive pattern in which there is a strong tendency to develop, among other malignancies, malignant melanoma. This disorder is Xeroderma Pigmentosum. It may be that the family reported by Anderson and colleagues is another such type of disease, and so distinct from other familial malignant melanoma. Certainly the other families in this report, as with those studied in our series, show no similar pattern of inheritance.

TABLE 3. *A Comparison of the Age at Menarche and Menopause and of the Fertility of the Women in the Groups Studied*

	Control Subjects	Familial Group	240 Cases of Melanoma
Average age at Menarche	14.19 ± 1.46	13.34 ± 1.27	13.98 ± 1.45
Average age at Menopause	45.50 ± 4.27	47.63 ± 2.85	47.92 ± 4.30
Average number of Children	2.57 ± 2.49	3.34 ± 2.49	2.49 ± 2.11

Certain features of familial malignant melanoma, first emphasized in the paper by Anderson and colleagues must now be regarded as established. These features are the tendency to develop multiple primary malignant melanomas among the affected members of the families and the very early age at which the malignancies appear in many of these families. These points have been confirmed in our study. The maximum number of primary malignancies in any one patient in our series was believed to be eight, the patient having lost count of the number of lesions over a span of more than a quarter of a century, while the youngest affected patient was a boy of 13 years. Neither the site nor the type of lesion has been reported to have any specific features in familial instances reported to date. Our evidence that melanoma in familial cases is no more likely to occur in any one area of the body than another would be in keeping with an endogenous origin of the malignancy in these cases. Hereditary factors concerning the development of melanomatous tumors in animals have been studied in several species and are known to exist in fish, salamanders, hamsters and pigs.[15] The dappled grey horse is known to be particularly prone to develop malignant melanoma because of the grey color which is due to a dominant allele segregating in Mendelian ratios, perhaps with some diminished fitness distorting the numbers. The inheritance of a tendency to develop malignancy of a nonspecific type has been much debated over a long period of time, with no finality to the argument. Possibly no better summation has been made than that of Schull[16] who pointed out that the results of studies to determine

TABLE 4. *A Comparison of Deaths from Malignant Disease Excluding Melanoma among First Degree Relatives of Familial Cases of Melanoma*

		Deaths from Cancer	Other Deaths
Males	Observed	10	42
	Expected	8.13	43.87
Females	Observed	17	35
	Expected	8.54	43.46

♂: $x^2 = 0.53$, $0.5 > p > 0.3$
♀: $x^2 = 10.02$, $0.01 > p > 0.001$

whether cancer is inherited have elicited merely the conjecture of a geneticist based upon the basic principles of genetics. Namely, similar to most other traits a tendency to develop cancers of many specific types can be shown to be prevalent in families with a low empiric risk of any individual in that family to develop the specific tumor to which the family is prone. The dramatic forms with Mendelian inheritance such as polyposis coli, neuroblastoma, tylosis with esophageal cancer, and so on are exceptions to the rule. Nevertheless, in research one does not always find what reason would lead one to expect; this is the fascination of the endeavor, and the rationale for further investigations. The interesting recent report of Swift[17] on the tendency to develop malignant transformation in the near relatives of patients with Fanconi's anemia is very apposite in this context.

Conclusion

In conclusion, our findings have demonstrated that there is a real genetic element among the factors responsible for the causation of malignant melanoma in Queensland. This genetic contribution is almost certainly not the result of a genetic polymorphism at a single locus, but appears to show many features found in polygenic inheritance. We believe that inheritance of a slight tendency towards malignant melanoma does occur; it is not dominant, recessive or sex-linked, but is the result of the additive contribution of an undetermined number of alleles at separate loci. Although a familial environment may be a contributing factor it would seem that this factor cannot entirely explain the observed familial patterns.

It would appear that there is a racial difference in susceptibility to develop the disease in Queensland, people of Scottish and Irish ancestry being more prone to show familial aggregations of cases. We were unable to demonstrate any particular inherited feature that carried with it a specific increased tendency to malignant melanoma. In particular, pigmentation of skin, hair, eyes etc. did not appear differently distributed among our familial melanoma cases from the pattern found in a closely matched control group. The curious and inconclusive incidental observation of frequent records of malignancies of many other types involving many other tissues among the relatives of these familial cases warrants investigation further.

Summary

A study of the pattern of inheritance and of the clinical features and personal characteristics of the patients in 42 kindreds affected by malignant melanoma has been carried out using data collected by the Queensland Melanoma Project. The pattern suggested the influence of a polygenic form of inheritance, but environmental factors common to the family concerned, together with chance association of patients played a part in the final picture. Familial patients tended to be younger; they had multiple primary lesions and were of Scottish or Irish descent. There was no suggestion that a separate form of malignant melanoma with a recognizable Mendelian pattern of inheritance and separate clinical and histologic features was responsible for the familial instances.

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Problems of Verrucose Squamous Carcinoma

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VERRUCOUS SQUAMOUS CARCINOMAS have many points of dissimilarity from squamous carcinoma in general. Most arise from moist squamous surfaces shielded from light. The lesion usually supervenes on a long-standing plaque of leukoplakia. After a papillary exophytic stage, which may be prolonged, it eventually invades by regular extensions of its deeper markedly filiform pattern. This continuity of surface may be retained even when penetrating deeply, for example into mandibular bone. A fine hyaline basement membrane is often induced, or produced, around these penetrations and organoid sequential development of the squamous cell sheets is minimally abnormal. Consequently, from the pure microscopic appearances of bite biopsies in this phase diagnosis is extremely difficult for pathologists. It is a main purpose of this report to discuss these problems and our experience in 33 cases (Tables 1 & 2).

By contrast, the clinical appearance of these lesions is characteristic, so that once known there is room for little doubt. Distant metastasis is rare no matter what the size of the lesion, its depth of local penetration, or after durations of up to three decades. The commonest natural history is one of relentless slow growth, very frequent recurrence after operation, marked inflammatory reaction around deeper disintegrating keratinizing penetrations, and a considerable failure to respond to radiotherapy. As it tends to occur in the mouth, larynx, or perianal sites the cumulative problems in diagnosis and treatment are formidable. Consequently it is regrettable that the lesion is seldom mentioned in textbooks, permitting an untenable conclusion that it is almost benign.

Sites, Modes of Spread, and Synonyms

The majority of instances so far reported have occurred on the inner surface of the cheek along the bite line, or on the gingiva. Many authors have noted a preliminary flat plaque of leukoplakia, which may endure for as long as 10 years before the characteristic white filiform verruca appears (Figs. 1, 3, 4). After the initial flat leukoplakic phase, the filiform wart may very slowly invade later on a broad front into underlying tissues. The dense inflammatory reaction does not appear until the deepest invasions of these filiform ridges disintegrate, exposing keratin. Bite biopsies through such a lesion, well organized superficially, without knowledge of its true depth may then be indistinguishable from pseudoepitheliomatous hyperplasia. The perianal lesions are prone to be regarded as *refractory chronic hydradenitis*.

The patient often complains of a persistent soreness in either leukoplakic or filiform lesions. Lymphadenitis is commonplace in the region, and suspected to be metastatic. Long periods of dormancy may occur but growth is usually very slow and equally relentless. Similar verrucous carcinomas have been reported with lesser frequency on the columella of the nose, in maxillary sinuses where they may bore eventually through the hard palate, in the larynx[14] in which severe obstruction is produced and direct invasion of the thyroid may follow (Fig. 8), in the esophagus,[15] and also in the bronchi. The latter was reported as a locally destructive form of non-metastasizing bronchial papillomatosis.[5] In retrospect and re-

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view it is a verrucose carcinoma. As has been reported by Moore and Lattes,[17] independent lesions may occur in various pulmonary lobes separated in incidence by as long as three decades. For this reason conservative resection in that location becomes essential.

Verrucose carcinomas have also occurred on the scrotum, vulva and perianal regions in which they may cover a wide area. In the latter the appearances may be verrucose, or may simulate multiple fistulae. In rare instances they have occurred on the penis, cervix and

TABLE 1. *Sites of Verrucose Carcinoma*

Inner Lip	7	(21%)
Remainder of Mouth	11	(33%)
Columella	2	
Maxillary Antrum	1	
Larynx	3	
Peri-anal	4	(12%)
Cervix	1	
Vulva	1	
Scrotum	1	
Penile	1	
Leg	1	

TABLE 2.

Length of History	Site of Lesion	Number of Recurrences	Responses to Surgery and Radiotherapy
1. 16 yrs.	Leukoplakia of lower lip, becoming verrucose in 6 years.	9	(1) After 7th recurrence following excision was given 4550 rads at 200 k.v. in 17 days. (2) Recurred and was given 4200 rads in 11 days. (3) Recurred. Had excision ant. 1/3 alveolus and lower lip. No recurrence in 5 years.
2. 27 yrs.	Wart on left lower lip, recurring and extending into cheek mucosa.	7	(1) Recurrence after first excision, implanted with 60 mg. radium with 0.5 mm. Pt. filtration 4½ hrs. (2) After fifth surgical re-excision given 4000 rads in 16 days at 280 k.v. No recurrence in 5 years.
3. 37 yrs.	Leukoplakia of right tonsillar pillar "treated with radium", 30 years before papilloma appeared on right tonsillar pillar.	0	(1) Given 5580 Co^{60} in 41 days. No recurrence in 7½ years.
4. 5 yrs.	Papillary penetration of hard palate from right antrum dislodging denture.	0	Infraorbital maillectomy followed by Radium mould in antrum with 4000 rads at 0.5 cm. No recurrence in 5 years.
5. 6 months	Verrucous lesion floor of mouth to right frenulum.	0	12 radioactive gold seeds implanted over 2.7 cms. delivering 7700 rads to area. Lesion disappeared.
6. 4 yrs.	Leukoplakia under tongue, becoming verrucose 4 years later.	9	(1) Nine diathermy and surgical excisions. (2) Then given 6600 rads Co^{60} in 30 days. Recurred in alveolus in 4 months and cheek sloughed. (3) Given 4800 rads Co^{60} in 25 days to new marginal recurrence in central alveolar region. Died 4 months later in congestive failure.
7. 4 yrs.	Rapidly extending wart on right columella. Blocked nares and destroyed septum.	Unhalted progression	In 2nd year was given 4000 rads in 27 days at 250 k.v. 2000 rads in 9 days at 140 k.v. 7200 rads Co^{60} in 36 days 3600 rads Co^{60} in 16 days Lesion progressed to complete destruction of nose, upper lip, lower eyelids; without metastases at death 2 years later.
8. 20 yrs.	Leukoplakia left cheek with slow appearance of wart extending on to lips and spreading through full thickness.	5	Recurred slowly after 5 cautery and surgical excisions. 4200 rads Co^{60} in 47 days produced marked regression. Died 2 months later. No autopsy. (Fig. 2.)
9. 5 yrs.	Small verruca extended over whole right cheek and to adjoining gingiva, over 3 years in an 81 yr. old edentulous female.	2	(1) 5500 rads tumour dose of Co^{60} in 33 days produced disappearance. No recurrence in 2 years.
10. 2 yrs.	Became hoarse and papillomata seen obstructing lower larynx and upper trachea.	0	5600 rads Co^{60} in 41 days produced no regression. Verrucose carcinoma directly invaded thyroid and strap muscles. Died from respiratory obstruction. No metastases.
11. 14 yrs.	Persistent multiple peri-anal fistulae with verrucose carcinoma in walls. No signs of metastases.	Never healed	Repeatedly diagnosed as pseudo-epitheliomatous hyperplasia in anal fistulae. 2730 mg. hours radium with 1 mm. Pt. filtration in 10th year. Lesion regressed temporarily. Died 1 year later of unknown cause.

lower leg.[3] The patients were elderly. In our experience the patients had a mean age of 64 years, ranging from 43 to 84 years, if the cervical and penile instances are excluded. Both of these patients were young, being 20 and 28 years old respectively.

As the lesion penetrates, organoid arrangement in the verrucous pattern may be lost. Even when it is extensive, for example with direct invasion from the larynx into the thyroid lobes, distant metastasis remains rare. In the worst case which we have encountered the verruca began on the right columella. Over 4 years it progressed to complete destruction of the nose, upper lip and lower eyelids, and failed to respond to radiotherapy. Metastases still were not present at death.

Outstanding illustrations of the peculiar early mode of invasion by elongation of the very long filiform rete ridges have been reported by Kraus and Perez-Mesa,[14] by Ackerman,[1] Goethals *et al.*,[10] and Cook.[3] In all instances deep penetrations had occurred into the mandibular bone or had completely penetrated the cheek from the buccal surfaces. Knoblich[13] reported the same peculiar characteristic in a unique lesion which had replaced the lower rectal mucosa. Penetrations right through the rectal wall were lined by papillary squamous epithelium, again existing without distant metastasis or vascular or lymphatic penetration.

Descriptions of the lesion are fragmented through the literature under very descriptive synonyms which include "oral florid papillomatosis,"[11] "inverted nasal papillomatosis,"[2] "laryngeal florid papillomatosis,"[22] "cystic bronchial papillomatosis,"[5] "squamous carcinoma occurring in anal fistulae," and "giant condyloma accuminatum of Buschke-Löwenstein."[13]

Causes of Under Diagnosis in Microscopy

This is a rare example of a consistently superior clinical diagnosis of a neoplasm, reflecting real diagnostic problems in microscopy. These are so marked that the relative frequency of the lesion for various sites is uncertain.

In a classic article in 1948, Ackerman[1] noted that there was "downgrowth of fingers of epithelium. As the process continued, club shaped fingers of hyperplastic epithelium gradually push rather than infiltrate their way into deeper tissues. It should be emphasized that this epithelium is well differentiated and that the basement membrane remains intact." It is around these observations that the main difficulties for pathologists are still centered.

The maintainence of a continuity of zig-zag surface by very long filiform processes has been referred to (Figs. 3 & 5). These may sometimes reach almost 2 cm. in amplitude and persist even into true invasions extending on a broad front for example into mandibular bone. As a clearly defined very thin hyaline basement membrane can be detected surrounding some, but not all, of these deeply intruding rete ridges, many authors have avoided calling this invasion. By the time of deep penetration this may be evident clinically.

"Intactness of basement membranes" has been used widely, for example especially in squamous carcinoma of cervix, to determine whether a lesion is *in situ* and still in a safe clinical state. However, investigation of subepithelial basement membranes by Revel and Hay[21] has shown that epithelium plays the major role in their production. Grobstein[11] has also shown that primitive ectoderm seems to produce a monomer necessary for the final production of collagen in the underlying dermis, by polymerizing action in adjacent mesoderm. This change

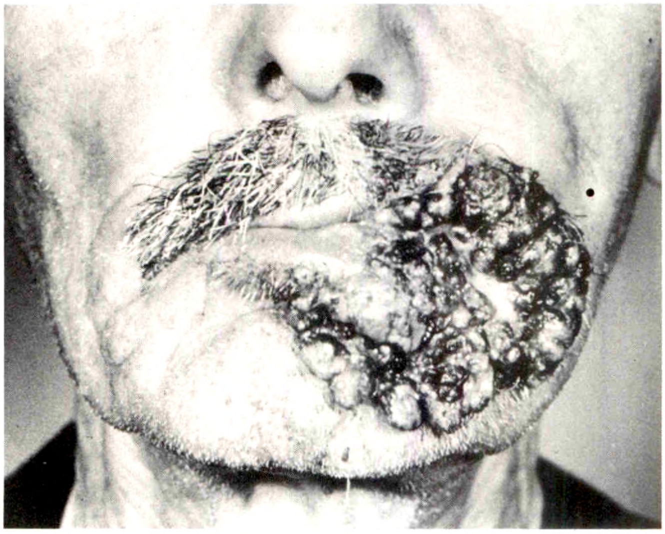

FIG. 1. Case 8. After 7 years dormancy a papilloma on buccal aspect of upper lip expanded and infiltrated whole thickness of commissure of cheek. Biopsies were read as "papilloma with demarcating basement membrane," and "pseudo-epitheliomatous hyperplasia."

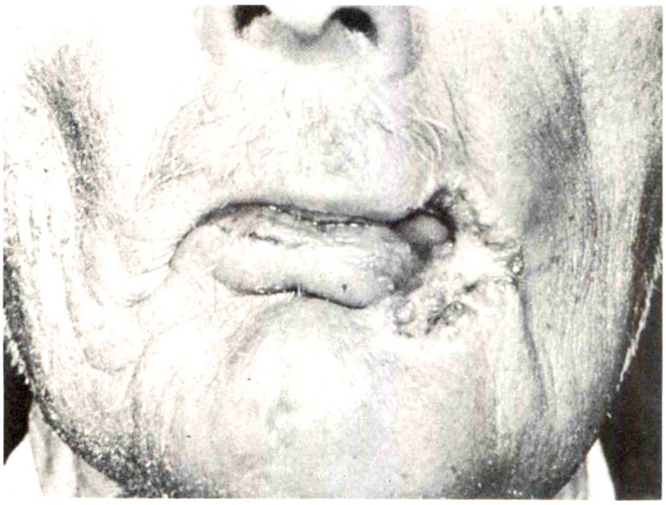

FIG. 2. Case 8. Marked regression, produced by 4600 rads. Co^{60} given over 47 days, unmasks destruction of cheek.

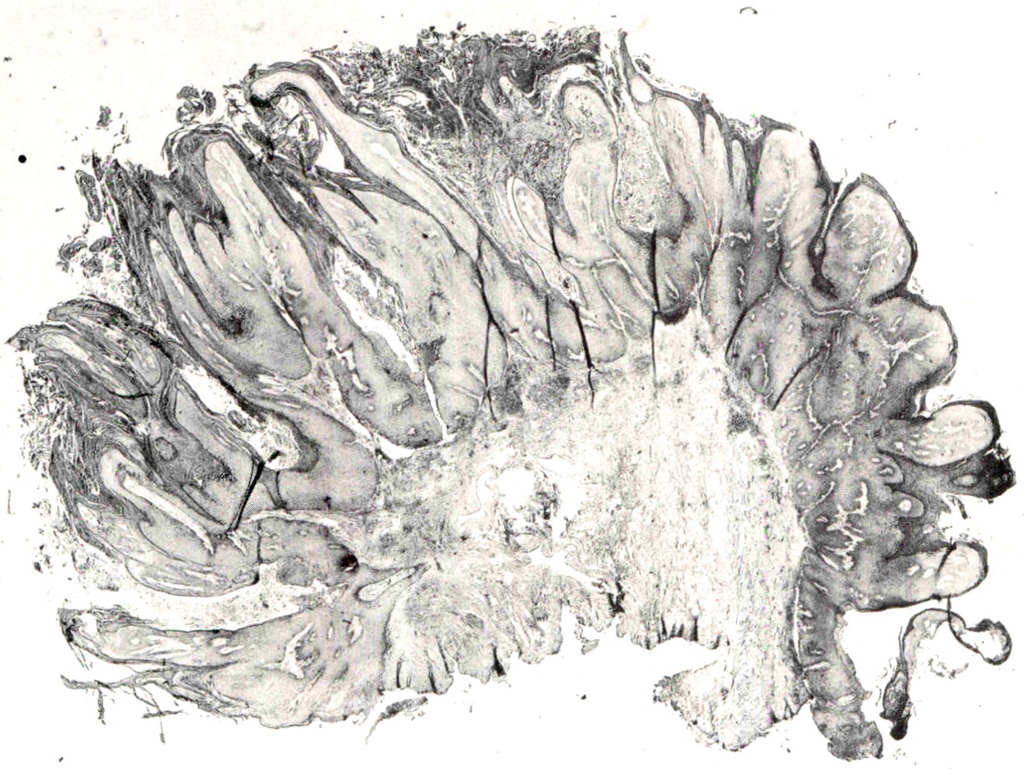

FIG. 3. Case 8. Blunt intrusions of well polarized epithelial tongues, maintaining a surface, with fine basement membranes, simulating benign papillomatosis.

in the concept of epithelial basement membrane from a purely passive barrier-layer, into a functional product of epithelium, has altered the pathologic basis for detection of micro-invasion.

When intactness of basement membrane has been used as divider between *in situ* carcinoma of cervix and micro-invasion, it has proven to be a serious pitfall. In various series an interpretation of micro-invasion, using this feature, has ranged[6] from 63% to 5%. Long clinical follow-up has favoured the latter proportion, and suggests that patchy loss of basement membranes in that condition and site is common and not significant by itself alone. For example Fidler[6] reinterpreted his own extensive series of intraepithelial carcinoma of cervix reducing the proportion of micro-invasion from 10% to 6%, by using other criteria. In a similar consideration of the limited dermal invasions of keratoacanthoma, Montgomery[16] states that "whether the basement membrane is intact or not is of little diagnostic significance." The deepest invasions of the rete peg tips in keratoacanthoma also show a strong and characteristic tendency to degenerate. On biopsies these are difficult to distinguish from carcinomatous invasion. However, in keratoacanthoma the invasive process always stops short just superficial to the depth of the sweat gland coils. Also the lesion occurs in hairbearing sites, unlike the majority of verrucose carcinomas so that the two lesions seldom have to be differentiated in practice.

Verrucous squamous carcinoma induces or produces its own basement membrane around some of the tongues of true invasion[1,4,8,10,14] (Fig. 7). The presence or absence of a basement membrane, thus, cannot be used as a reliable criterion of non-invasion. This neoplastic epithelium appears to be able to continue a normal inductive or productive function in its filiform phase.

When we turn for aid to cytologic characteristics the abnormalities are often high power minutae, and this again contrasts with the ease of clinical diagnosis. It is worth studying a number of known examples, for Foye *et al.*[8] summarized a general experience that "nuclear anaplasia is minimal and mitotic figures are hard to find." Some anisonucleosis and nuclear enlargement is nearly always detectable in the apparently normally polarized filiform processes, and the nucleoli are abnormally prominent (Fig. 6). While sequential development of squamous cells produces an almost normal appearance, mitotic activity is moderately increased but not uniformly. Mitotic figures tend to occur in tiny loose clusters, and may be present above the juxta-basal layer. This feature should always alert us to the possible nature of the lesion.

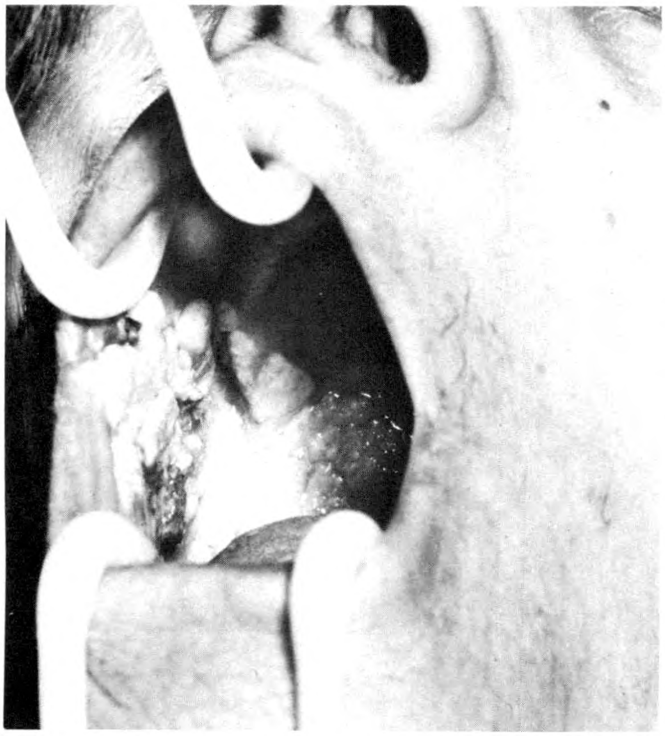

FIG. 4. Case 9. Fissured filiform exophytic phase arising in leukoplakia along bite line of cheek, and extension on gingiva.

So-called "premature cell keratinization," or patchy epidermidization occur but have not been, in our experience, invariable or helpful. Knoblich[13] pointed out that the superficial squamous cells were often vacuolated as in condyloma acuminatum which we confirm, but this is not diagnostic.

The difficulties with bite biopsies for pathologists are illustrated by the following sequence of diagnoses recorded in one of our cases and made by experienced general pathologists on pure microscopic appearances alone. The patient had a wart on the buccal aspect of the upper lip which slowly extended over 20 years. During the last 13 years the series of biopsies were reported as "pseudoepitheliomatous hyperplasia," "epithelial papilloma with demarcating basement membrane," "dyskeratotic papilloma without malignancy," "verruca senilis," and in the final year as "low grade infiltrating carcinoma in which it is difficult to distinguish infiltration." During the last 3 years, the lesion penetrated the whole thickness of the cheek clinically and the surgeon's diagnosis was unequivocal.

In initial biopsies, unless the pathologist was very much aware of this lesion, review of our records show the following diagnostic dilemmas "papillary intrusions

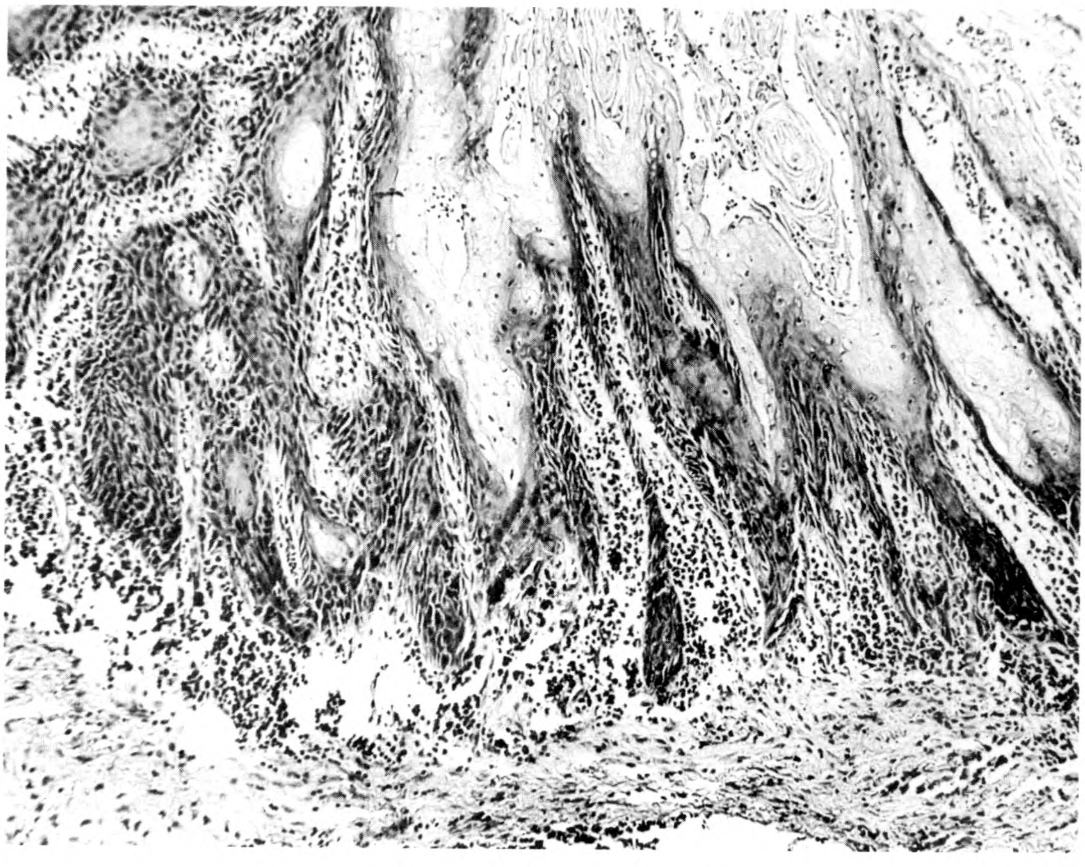

FIG. 5. Early verrucose squamous carcinoma. Clinical obstructive laryngeal "papillomatosis." The rete ridges are invading by fine elongations. The deep inflammatory phase is appearing, simulating pseudoepitheliomatous hyperplasia.

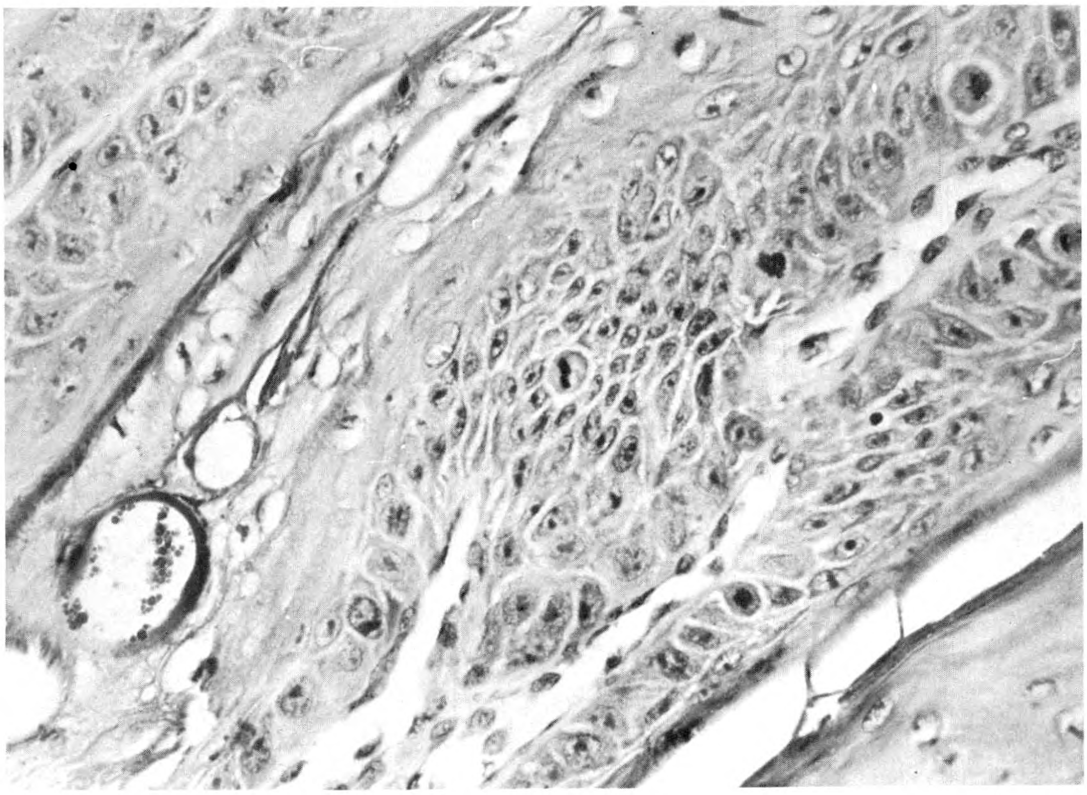

FIG. 6. Verrucose carcinoma of alveolar ridge. Squamous cells at all levels show nuclear and nucleolar enlargement and irregularity on high power. Patchy mitotic activity is present.

into the dermis but with a degree of epithelial differentiation which does not permit microscopic diagnosis of squamous carcinoma," "senile verruca with epithelial downgrowths on which definite malignancy cannot be diagnosed," "benign infiltrating squamous papilloma," and "epithelial hyperplasia without significant dysplasia showing aggressive acanthosis and therefore compatible with verrucous carcinoma." With this lesion the pathologist is wise to visit the patient, in consultation, and see the exact relative depth from which the biopsy was taken.

In the later stages of invasion when filiform organoid arrangement is lost, inflammatory reaction around disintegrating invading epithelium is intense. When read without clinical information on pure microscopic appearance this inflammatory phase closely mimics pseudoepitheliomatous hyperplasia. In perianal site it is often regarded as "refractory hidradenitis" (Fig. 9).

The Role of Carcinogens

In the first series of verrucous squamous carcinomas, lesions were reported to have occurred in the mouth. This led to some incrimination of tobacco through a peculiar chain of circumstances.

Buccal carcinoma had long been observed in Southeast Asia among tribes who also habitually chewed and carried a quid in the cheek pouch. However, as Orr[18] pointed out in 1933, oral carcinoma was of low incidence among tribes of Travancore who chewed betel nut alone. It was of high incidence among other tribes who chewed tobacco, with or without the betel. In 1941, a possible role for chewing tobacco as the local self-applied carcinogen was reported by Friedell and Rosenthal,[9] in a series of patients from the southern U.S.A. who had "papillary verrucoid carcinoma" of mouth. This was the initial report of this lesion as an entity.

Ackerman[1] gave the first detailed description of the unique characteristics of verrucous carcinoma in 1948, again from buccal sites in patients from the southern United States. This remains the classic article. Seven of the 18 patients were not inveterate tobacco chewers. Similarly in the Mayo Clinic series of 55 cases reported by Goethals,[10] only seven were habitual tobacco chewers. In our series, only one of 24 patients with buccal or respiratory verrucose lesions reported such a habit. When reports of the same pathologic entity appeared for nasal sinuses, larynx and bronchi, and finally for penile, scrotal, vulval, perianal and lower rectal areas it was clear that tobacco could not be the local carcinogenic agent for all.

Those reports[23,24,25] recording the oral lesions as "snuff dippers' or tobacco chewers cancer," are nearly all concerned with patients from parts of the United States, in tobacco growing areas and areas in which the habit is prevalent in the elderly. It seems likely that the coincidence of a very common habit is entangled with the pilot reports in which the peculiar characteristics of verrucose squamous carcinoma were first decided.

Treatment

It is difficult to assess the success of surgical treatment in such an indolent disease, which often reappears slowly. The 5-year survival rate in Goethal's[10] series was 76.4%. However, long survival produces problems, for the neoplasm is difficult to extirpate surgically. Most of this difficulty lies in determining microscopically the extent of the dysplasia around the margins of the overt filiform phase. In our experience filiform recurrences appear sometime within 4 years. They grow typically around the margins of the excised area like a wreath (Fig. 1). The sole exception to this time relationship was reappearance of a verrucose carcinoma of the scrotum. However, it arose in another scrotal area 10 years after the first excision.

Twelve of our 33 patients had one or usually more recurrences. One instance in the larynx could not be controlled by local surgery or radiation and the patient died. Another patient with extensive perianal lesions had temporary regression with radium and refused further

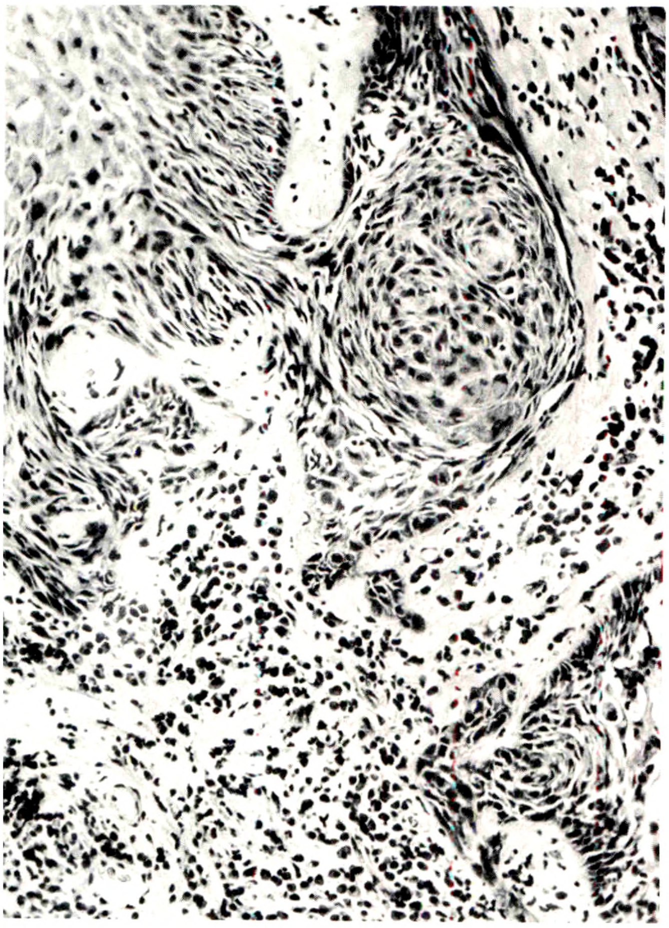

FIG. 7. Case 1. Deeper filiform invasions of inner surface of lip etaining organoid arrangement and with formed homogeneous asement membranes.

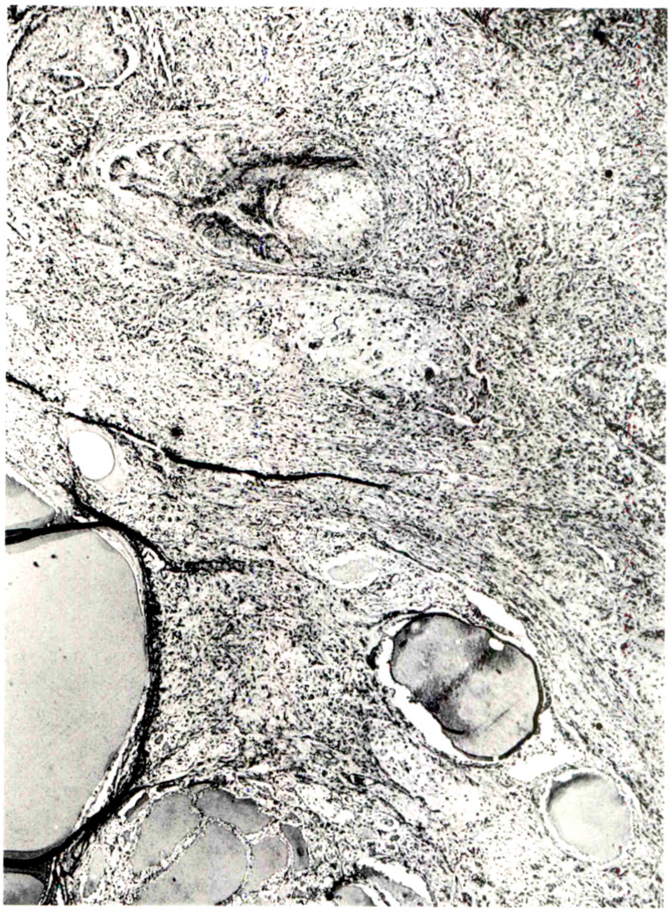

FIG. 8. Case 10. Verrucose carcinoma of larynx losing papillary organization as it invades thyroid.

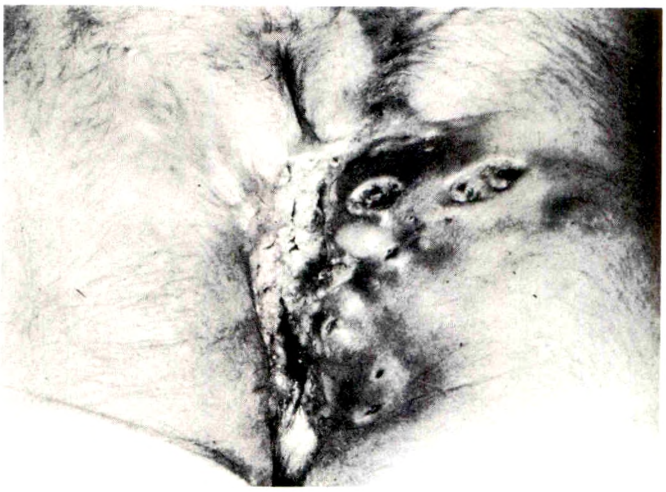

FIG. 9. Case 11. Warty excrescences form the walls of multiple persistent penetrating perianal fissures simulating chronic hidradenitis.

treatment. The remainder appeared to be cured by local sugical excision since metastasis is not expected.

Metastasis did not occur in any of our patients. A radical vulvectomy and abdominal perineal resection for extensive lesions, in vulva and anal sites respectively, did not show any node involvement in either case. In the laryngeal verrucous carcinoma which invaded the thyroid, the penetrations were of higher microscopic grade, but without metastasis. As with Profitt's[20] series, transformation into higher grade or metastasizing tumor did not occur after repeated operation. On the other hand, Goethals *et al.*[10] reported development of a separate but metastasizing squamous carcinoma in the same anatomical region in six of 55 patients.

Transformation into metastasizing anaplastic and spindle cell types has been reported in three of eight patients by Perez *et al.*[18] These lesions appeared after latent periods of 2 to 8 months, following external radiotherapy, two with super voltage therapy. Fonts *et al.*[7] reported a similar transformation in three of eight patients after external super voltage radiotherapy. A variety of radiotherapy, as available, had been used in our patients over the years, but such transformation was not seen (Table 2).

Failure to control the lesion by radiotherapy has been reported frequently. Ackerman[1] in 1948 reported eight cases in which it failed, and recurrence required operation in seven. In our experience radiotherapy can cure if the dysplastic area is delineated and treated initially with a heavy delivered dose. As will be seen from Table 2 anything less, or repeated smaller doses, are likely to fail.

Kanee[12] has reported disappearance of oral lesions, which had recurred after surgical therapy using methotrexate locally in one instance. Further trial will clearly be of much interest.

Summary

Verrucose squamous carcinoma is very difficult to diagnose microscopically except when advanced. Clinically it is unmistakable at any stage. The presenting white filiform verruca slowly invades its base, even into bone, by an exaggeration of its zig-zag pattern. While maintaining this apparently benign continuity of surface, it often induces or produces basement membranes which mask true invasions. Intact basement membrane therefore cannot be used to separate the *in situ* from an invasive stage. In the third phase this filiform organization is lost. A marked inflammatory reaction is provoked, apparently around exposed keratin. This picture is easily confused with pseudoepitheliomatous hyperplasia on bite biopsy. In perianal sites this lesion may be diagnosed clinically as "refractory chronic hidradenitis," or "papillomata occurring in fistulae."

Most instances arise on mid-line surfaces, which are excluded from light but squamous in type, such as mouth, respiratory tract, perianal and vulval sites. Association with tobacco chewing as a local carcinogen appears variable and coincidental. No matter what the extent of the lesion, and with durations up to several decades, metastasis remains rare. However, local destruction is eventually severe. In the series of 33 cases reported, one-third recurred one or more times after attempted surgical excision. Cure or control by radiation was ineffective, unless heavy dose was delivered to the dysplastic zone. This is not necessarily confined to the filiform verruca, but in a surrounding flat or leukoplakic rim. Therefore, recurrences are typically circumferential and wreath-like.

The causes of microscopic underdiagnosis are reviewed, together with features which differ markedly from those of squamous carcinoma in general.

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Pulmonary Reimplantation Response

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REIMPLANTATION or autotransplantation of the lung is a formidable procedure involving division of many structures. In the past, reimplantation of the canine lung presented technical problems which resulted in high surgical mortality and appreciable compromise of the bronchial and vascular anastomoses with consequent functional impairments in surviving animals.[3,6,11,18,20,24] Recent technical improvements have made it possible to minimize defects at the bronchial and vascular anastomoses;[2,22] a reimplanted lung can now recover normal morphology and function remarkably well if the bronchus and major vessels are adequately reconstructed.[10,20,23] After technically flawless reimplantation, however, functional defects may occur in the early postoperative period. These defects are largely reversible[13,21] and may be attributed to disruption of nerves, lymphatics and bronchial vessels and/or to ischemic injury.[1,7,12,18]

We have been investigating the mechanisms of pulmonary allograft rejection in dogs using serial chest roentgenography and pulmonary angiography with simultaneous lung biopsy.[15,16] Serial chest roentgenography is an important means of monitoring the status of the allograft in the postoperative period. Since the anticipated responses to autotransplantation have not been adequately defined, it may be difficult to determine whether a postoperative pulmonary roentgenologic abnormality is due to rejection or reimplantation. The present study was undertaken to allow us to establish the radiologic and histologic manifestations of pulmonary reimplantation.

Methods

Reimplantation of the left lung was carried out in eight mongrel dogs. Details of operative technic and perfusion were similar to those described elsewhere.[21,22] The pulmonary artery was divided obliquely and reconstructed by use of a meticulous technic which approximated 1 mm. bites of vessel wall with each stitch.

Four animals received 2–3 mg./Kg./day of azathioprine, 2–4 mg./Kg./day of prednisone, and rabbit anti-dog lymphocyte serum. The latter agent was given in doses of 10–20 ml./Kg. three times preoperatively and daily postoperatively for 2 weeks. The other four animals were not treated.

During the postoperative period, frontal (posteroanterior) roentgenograms of the chest were obtained daily of the unanesthetized animals in the prone position. Extensive examinations were performed on each animal on four occasions: in the early postoperative period (day 1–3), 1 week postoperatively (day 7–9), 2 weeks postoperatively (day 14–16), and 3 to 4 weeks postoperatively (day 22–31). The animals were anesthetized with intravenous pentobarbital and plain chest roentgenograms were obtained in the frontal (anteroposterior) and right posterior oblique (supine oblique) projections. A polyethylene catheter with side holes was then introduced into the right jugular vein and guided under fluoroscopic control into the main pulmonary artery. Serial angiograms were then obtained with the animals in the right posterior oblique position, using 1.75 ml./Kg. of 60% methylglucamine diatrizoate injected at

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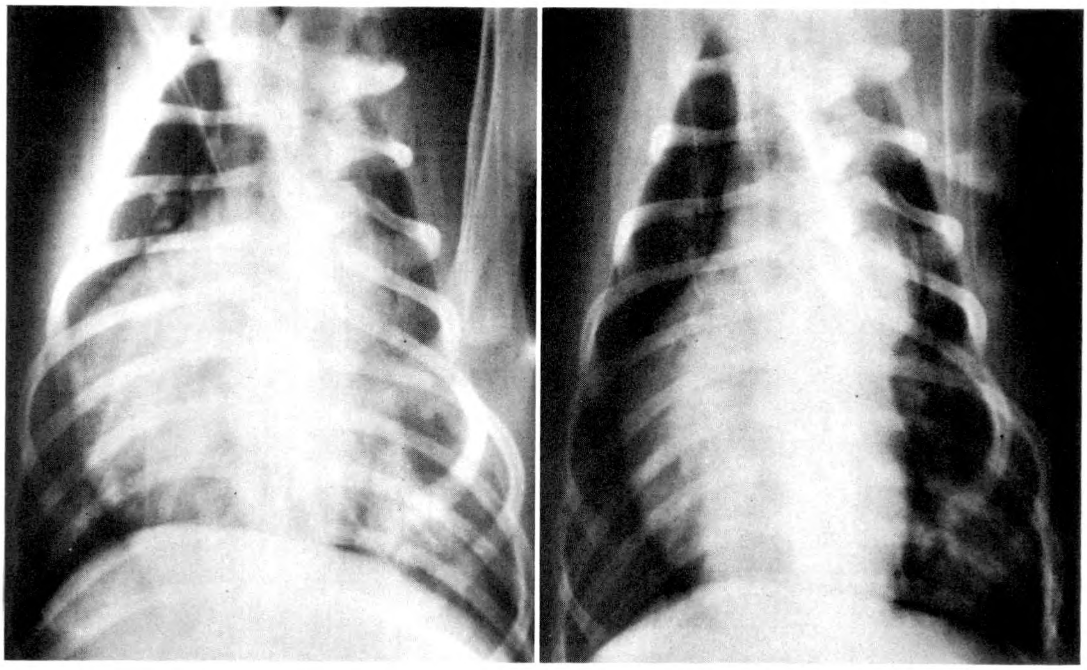
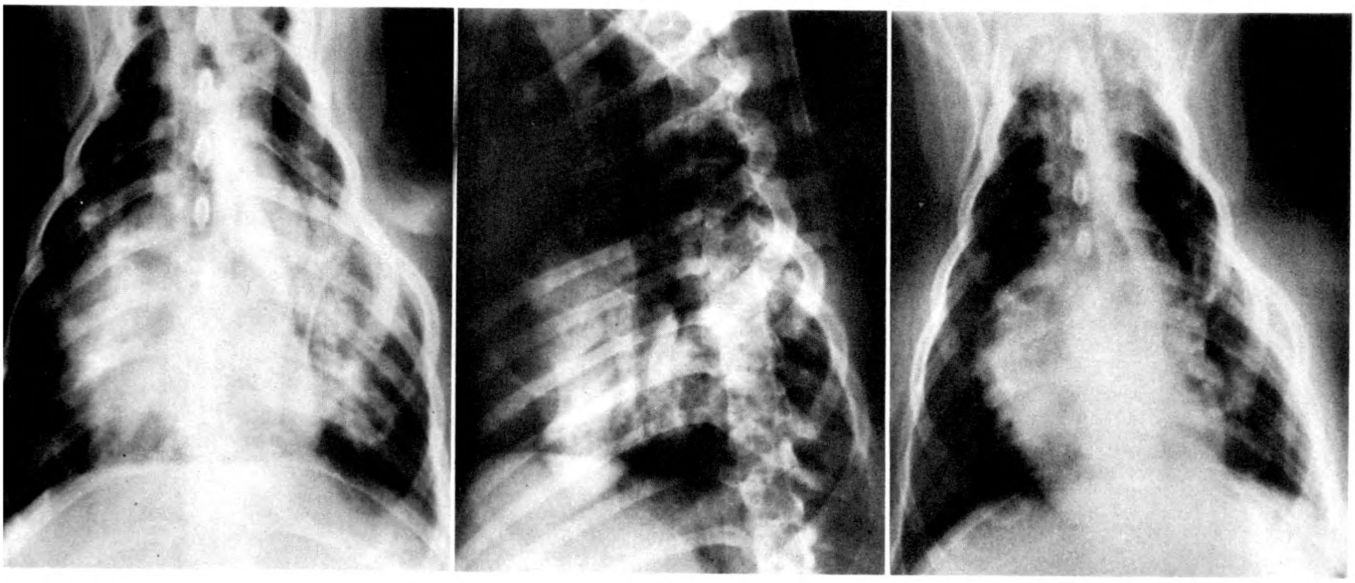


IG. 1. Usual reimplan-
ation response. Chest
oentgenograms following
utotransplantation of the
eft lung. Dog 1. (A.
eft) Second postopera-
ive day. The left lung
ontains an alveolar in-
ltrate in the diaphrag-
natic (lower) lobe and
n the central portion of
he upper lobe. A linear
lensity at the left cardio-
hrenic angle represents
hickening of the inferior
spect of the major pleu-
al fissure. The peripheral
nargins of the lung are
ormal. (B. right) Elev-
nth postoperative day.
he infiltrate has cleared
ompletely. Slight pleu-
al thickening persists.

rate of 15–20 ml. per second with filming at the rate
f two films per second for 8 seconds. Following the
ngiographic examination, thoracotomy was performed
nd the left lung was inspected and biopsied. All biopsies
vere fixed in formalin, embedded in paraffin, and stained
vith hematoxylin and eosin.

After the fourth examination, the animals were sacrificed and autopsied. The lungs were examined grossly. All anastomoses were inspected from within. The lungs were then fixed by inflation with and immersion in formalin. Multiple sections were taken and stained with hematoxylin and eosin.



IG. 2. Maximum reimplantation response. Chest roentgenograms following autotransplantation of the left lung. Dog 2. (A. left) Third
ostoperative day. Alveolar infiltrates are present in the proximal portion of the diaphragmatic lobe and the perihilar region of the upper
be. The infiltrate is bordered by a peripheral crescent of uninvolved well aerated lung. A curved linear density extending from the
iid portion to the base of the left lung represents thickening of the pleural fissure. (B. center) Third postoperative day. Right posterior
blique projection. The perihilar distribution of the infiltrate is demonstrated. (C. right) Seventh postoperative day. There has been ex-
ensive peripheral clearing. Some central perihilar patchy infiltrate remains in the upper and diaphragmatic lobes. The inferior aspect of
e pleural fissure remains prominent.

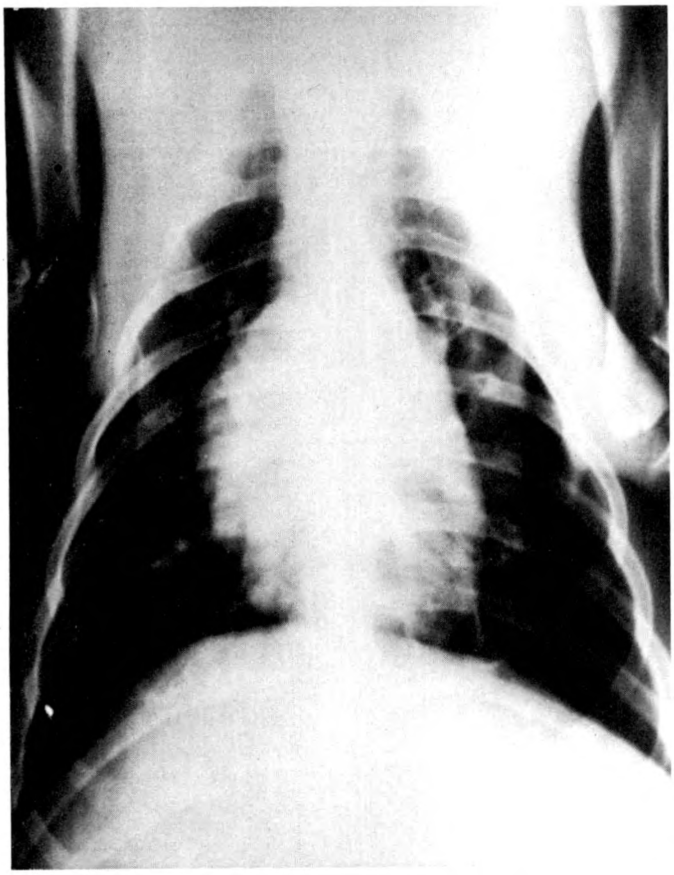


FIG. 3. Minimal reimplantation response. Dog. 3. Fifth postoperative day. There are minimal patches of infiltrate in the diaphragmatic lobe behind the heart and in the proximal portion of the left lower lobe. The chest roentgenogram returned to a normal appearance on the seventh postoperative day.

Results

The findings on chest roentgenography, pulmonary angiography and lung biopsy were the same in treated and immunosuppressed animals.

Plain Chest Roentgenography: There was a characteristic pattern and a definite timing of the roentgenographic abnormalities which appeared in the reimplanted left lung. The initial chest roentgenogram on the first postoperative day was always abnormal, although the degree and extent of abnormality varied. An alveolar infiltrate originated in the hilar region and extended into the proximal portions of the apical, cardiac and diaphragmatic (lower) lobes. On the second day the infiltrate coalesced as it progressed along a peribronchial and perivascular pathway to involve larger segments of the lung (Fig. 1A). The greatest involvement occurred on the third postoperative day when the lesions reached maximum development (Figs. 2A, 2B).

The areas of consolidation which constitute the pulmonary reimplantation response have the characteristics of *alveolar infiltrates.*[8,14] The lesions change rapidly during evolution; they follow a lobar pattern, and their margins are fluffy and vaguely defined. The *air bronchogram* phenomenon, in which the larger air passages are seen as linear radiolucent pathways contrasted by the opacified air spaces, is a feature of the lesion.

The segments of infiltration radiate from the hilum into a flame or fan shaped configuration with a limited peripheral extension. The outer third of the lung was always spared and a clear zone of normal-appearing pulmonary parenchyma surrounded the involved segments (Figs. 1, 2, 3). The most commonly involved area was the diaphragmatic lobe behind the heart (Figs. 1, 2, 6). The infiltrate never extended to the diaphragmatic pleural surface and hence the diaphragm remained in sharp definition. The second predilected site was the proximal portion of the apical lobe directly adjacent to the main pulmonary artery. The peripheral extension from this segment approached the pleural surface but a preserved crescent of clear lung always remained to demarcate the outer margin of the lesion. Thus the pulmonary autotransplantation response was never manifested by total consolidation of any lobe. Although there was no variation in the nature of the infiltrate in the autotransplanted lung, there was a considerable range in the degree of involvement. The roentgenograms illustrated in Figure 1 represent the usual response. The reaction of maximum magnitude is shown in Figure 2. In several animals the pulmonary reimplantation response was confined to a minimal patchy infiltrate in the diaphragmatic and upper lobes (Fig. 3).

The roentgenograms also contained evidence of reactive pleural change. An oblique, vertically oriente linear density at the medial aspect of the lung ba represented thickening of the inferior aspect of t oblique fissure (Figs. 1A, 6A). Occasionally sm amounts of fluid produced increased prominence of t superior segments of the fissure manifested by thin, sharp linear densities adjacent to the hilum (Fig. 2A). A collection of pleural fluid yielding a detectable density lateral to the lung was an unusual finding seen in only one animal.

Following the peak reaction on the third postoperative day, the abnormalities in the chest roentgenogram gradually resolved at a variable rate. Three dogs exhibited extensive clearing of the infiltrate by the seventh postoperative day, three dogs showed slight to moderate clearing between the third and seventh postoperativ days (Fig. 2). In the remaining two animals no chang was detected during this period. After the seventh da there was progressive clearing of all residual infiltra The infiltrate receded centrally and the proximal perihi involvement was the last to disappear. Thus, comple dissolution of all abnormalities occurred between th seventh and twenty-first days. Despite the trauma

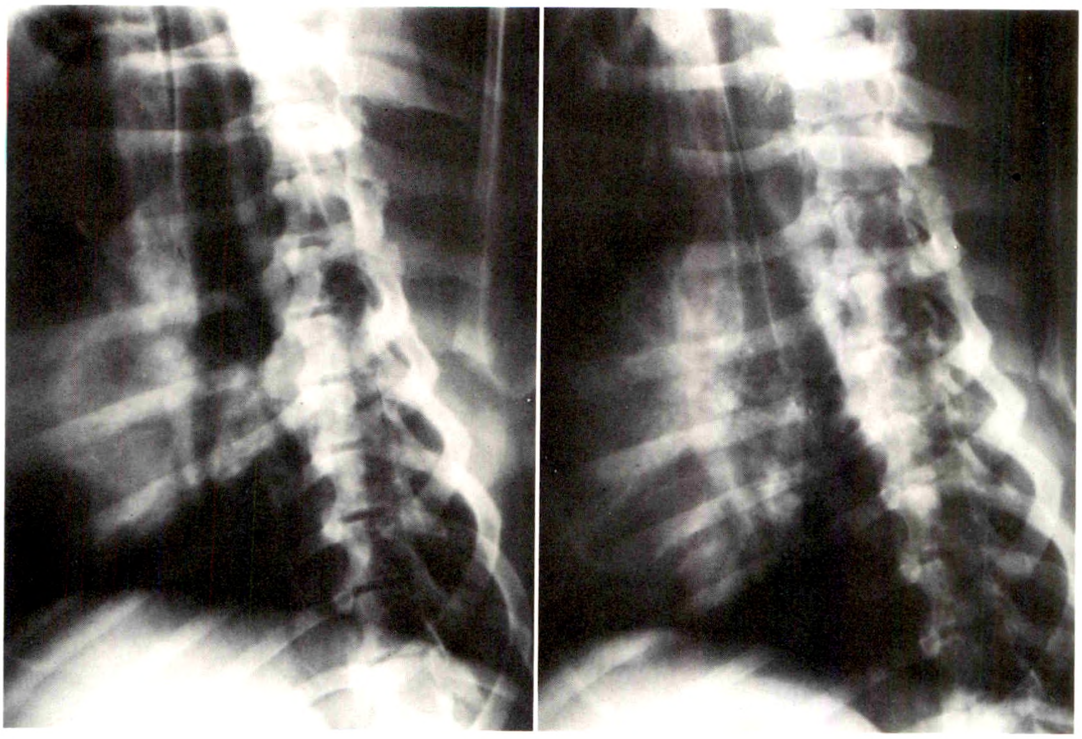


FIG. 4. Bronchial narrowing. Dog 4. (A. left) Right posterior oblique projection, fifth postoperative day. Narrowing of the proximal portion of the left main bronchus at the site of surgical anastomosis. (B. right) Right posterior oblique projection, 28th postoperative day. The lumen of the bronchus has returned to a normal calibre.

repeated thoracotomy and biopsies, the process of progressive reabsorption of infiltrate was never reversed; increase in pulmonary infiltrate in serial roentgenograms was never observed after the third postoperative day.

Plain chest roentgenography also offered a means of evaluating the bronchial anastomosis. The left mainstem bronchus is not well seen in frontal roentgenograms because it is obscured by cardiovascular structures. However, a series of four oblique plain chest roentgenograms (immediate postoperative, 1 week, 2 weeks, and 3–4 weeks postoperative) provided an opportunity to assess the contour of the air column in the proximal left bronchial tree. Narrowing of the lumen beginning at the site of the bronchial anastomosis was evident in each case. The magnitude of narrowing of the bronchial lumen was maximum in the first postoperative week when it

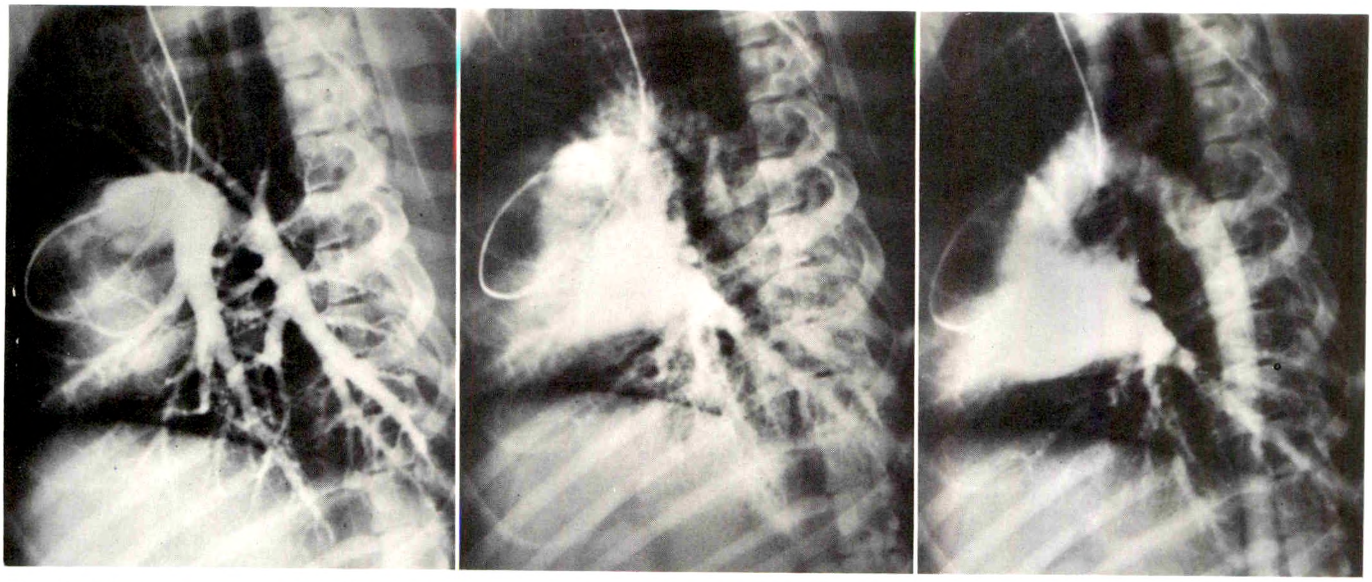


FIG. 5. Pulmonary angiography. Dog 2. (Same as dog in Fig. 2), 16th postoperative day. (A. left) Early arterial phase showing patent pulmonary arterial anastomosis and an equal distribution of contrast material to each pulmonary artery following injection into the main pulmonary artery. (B. center) Capillary phase. (C. right) Venous phase with filling of pulmonary veins of each lung, left atrium, left ventricle and aorta.

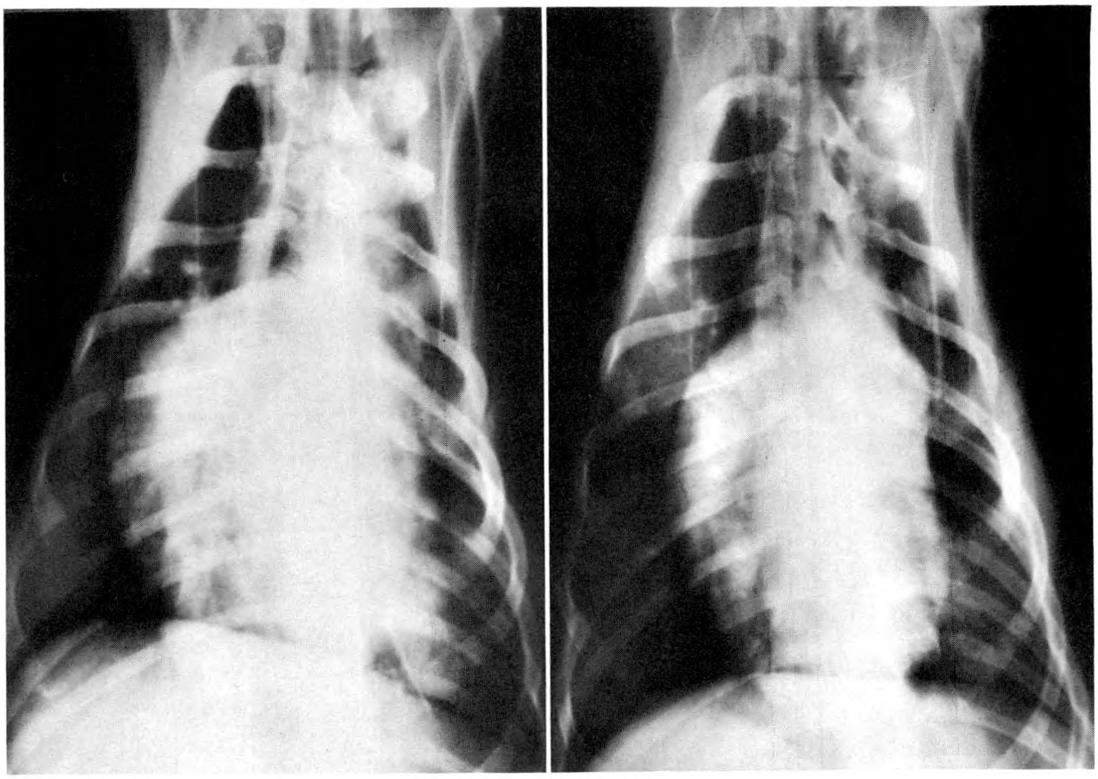


FIG. 6. Pulmonary reimplantation response in an allotransplanted lung. (A. left) Chest roentgenogram 7 days after autotransplantation of the left lung. There is a left lower lobe infiltrate and thickening of inferior aspect of the pleural fissure. (B. right) Same animal on the 14th postoperative day. The infiltrate has cleared completely.

approximated 50% of baseline measurements (Fig. 4A). The narrowing regressed considerably in the second week and a restoration toward a normal calibre bronchial lumen was noted in the third and fourth postoperative weeks (Fig. 4B). No significant narrowing was present at autopsy.

Pulmonary Angiography. Pulmonary angiography disclosed a patent pulmonary arterial anastomosis with no detectable narrowing (Fig. 5A), equal distribution of contrast material to each lung following injection into the main pulmonary artery, a normal capillary blush (Fig. 5B) and excellent filling and emptying of the pulmonary veins (Fig. 5C). The right posterior oblique position facilitates visualization of the junction of the left pulmonary veins with the left atrial cuff anastomosis.[9] No defects or obstructions were present at the anastomotic site. The angiogram remained normal throughout the study: the findings in the fourth week were no different from the findings in the immediate postoperative period.

Gross and Microscopic Morphology. Grossly the reimplanted lung appeared normal at all times when examined in the early and late postoperative period. Biopsies of the reimplanted lung in the early postoperative period (1-3 days) revealed traces of alveolar edema in six of the eight dogs. Biopsies of the remaining two animals in this period and all biopsies after this period were completely normal.

Discussion

The pulmonary reimplantation response consists roentgenologically of a coalescing alveolar infiltrate which is usually associated with and probably due to the presence of edema fluid within the air spaces. The process involves the central portions of the lung and extends into the pulmonary parenchyma along a peribronchial and perivascular pathway. The peripheral portions of the lung are not involved. The maximum expression occurs by the third postoperative day. This is followed by a variable improvement between the fourth and seventh postoperative days and a gradual disappearance of the infiltrate which is complete between the seventh and twenty-first days. The edema and resultant alveolar infiltrate are probably due to a combination of factors, the most important of which are ischemia, operative-trauma, and lymphatic interruption. During the clearing phase, the infiltrate recedes centrally so that the peripheral portions of the lung are the earliest to be restored to a normal appearance. The phenomenon of peripheral sparing and central regression may explain the discrepancy observed between the lung biopsies and the chest roentgenograms. In some animals the lung biopsies obtained from the outer third of the lung were entirely normal whereas the chest roentgenograms contained evidence of residual central pulmonary infiltrate.

The findings in our present study are consistent with the few published observations on the roentgenographic appearance of the autotransplanted lung. Trummer *et al.*[18] performed occasional roentgenographic studies on six dogs which survived more than 1 month following autotransplantation. They described progressive pulmonary opacification which became maximal on the third postoperative day. Thereafter sporadic chest roentgenograms revealed extensive clearing on the eighth to nineteenth days. The appearance of the autotransplanted lung in the baboon has also been studied at weekly intervals by chest roentgenography.[19] The findings were those of a diffuse alveolar process produced by edema and congestion which cleared gradually in a 4 to 6-week period. The variability between our results and those of others may be due to differences in technic or species variations.

The radiologic observations of transient alveolar infiltration and bronchial narrowing in the autotransplanted lung have their counterpart in physiological derangements which occur during the early postoperative period. The reimplanted lung exhibits a definite decrease in ventilation and oxygen uptake followed eventually by a restoration of normal respiration if all the anastomoses are functioning adequately.[5,13] In a recent study, a fall in autograft ventilation in the second and third postoperative days was associated with findings on inhalation scanning suggesting obstruction at the bronchial anastomosis.[4] Recovery of function began at the end of the first postoperative week and stable ventilation was restored at the end of the third week. Transient bronchial narrowing at the anastomotic site is presumably produced in part by the intraluminal protrusion of edematous bronchial mucosa. Extensive mucosal edema distal to the level of division of the bronchus has been observed by bronchoscopy of the reimplanted canine lung.[12] These findings would coincide with our observation of the appearance and regression of both bronchial narrowing and edematous infiltration of the air spaces. It has yet to be shown, however, that bronchial narrowing alone is capable of producing impaired ventilation. It is conceivable that the bronchial narrowing may represent the reflection of impaired ventilation due to other factors. In a separate completed study, serial postoperative plain chest roentgenograms and serial bronchograms were performed at weekly intervals following autotransplantation of the left lung in a different group of mongrel dogs.[17] The plain oblique chest roentgenogram has proved to be an effective means of assessing the status of bronchial anastomosis.

Our documentation of a characteristic radiological appearance of autotransplanted canine lungs must be considered in any comparable study of lung allografts. Obviously allotransplanted dog lungs will exhibit a reimplantation response. This has been the case in a group of dogs subjected to allotransplantation of the left lung that were treated with immunosuppressive agents and studied with serial chest roentgenography and lung biopsy.[15] In three animals, rejection was completely suppressed for several weeks. The roentgenograms and lung histology revealed the typical reimplantation response. In these dogs during the first postoperative week, a coalescing alveolar infiltrate was noted (Fig. 6A) while lung biopsy showed transient pulmonary edema. In the second week the infiltrate cleared completely (Fig. 6B).

Coalescing alveolar infiltrates in the allotransplanted lung which do not conform to the distribution or timing of the reimplantation response can be considered due to other disorders. Total consolidation of the lung in the first three postoperative days should lead to an investigation for thrombosis of the pulmonary arterial or venous anastomosis. The appearance of a new area of infiltrate or the extension of a previous infiltrate after the fourth postoperative day should be attributed to rejection or pneumonia. The infiltrates associated with rejection and pneumonia are more apt to extend to the outer third of the lung, thus producing total consolidation of an entire lobe, a phenomenon which has not been observed in successfully allografted lungs.

Summary

Chest roentgenograms, pulmonary angiograms and lung biopsies were studied serially in a group of dogs following reimplantation of the lung. Reimplanted lungs exhibited centrally located coalescing alveolar infiltrates immediately following operation. The infiltrate, which corresponded to pulmonary edema in lung biopsies, extended peripherally as it progressed to maximum expression on the third postoperative day. Thereafter abnormalities resolved at a variable rate with complete clearing between the seventh and twenty-first days. Transient narrowing at the bronchial anastomosis was also observed. Pulmonary angiography was entirely normal.

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Pulmonary Artery Catheterization in Critically Ill Surgical Patients

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In early 1970, Swan and Ganz introduced a flow-directed balloon tipped catheter for use in right heart and pulmonary artery catheterization.[14] It could be positioned with ease in the pulmonary artery by pressure-monitor and electrocardiographic control. The catheter became readily accesible for use in acute care units. Its utilization in patients with myocardial infarctions has attested to its clinical efficacy.

The present prospective study was undertaken to evaluate the use of the Swan-Ganz flow-directed pulmonary artery catheter in a variety of acutely ill surgical patients.

Materials and Methods

Fifty-three patients were included in the study. They were classified as in Table 1.

In all cases the catheter[†] was introduced by a peripheral vein upper extremity cut-down. It was then guided into position in the pulmonary artery by pressure-monitor control, as described by Swan and Ganz.[14] Position was then confirmed by chest X-ray. No catheters were left in the pulmonary artery more than 3 days. A solution of heparinized 5% dextrose (1,000 units in 250 cc./24 hrs.) was administered through the catheter when pressures were not recorded. The balloon was only inflated for wedge pressure determinations. Each catheter was used in only one patient.

Results

Group I: In the 30 cardiac surgical patients, pulmonary artery pressures were routinely monitored to assess their reliability, both clinically and radiographically, in determining the onset and progression of pulmonary interstitial edema, and thus of left ventricular failure. The following is a representative example:

Case Reports

Case 1. A 43-year-old man entered the hospital because of dyspnea on exertion and peripheral edema. He was known to have a heart murmur for 20 years, and had undergone closed mitral commissurotomy in 1961. Recently, pedal edema and end-flight exertional dyspnea appeared. He was taking digitalis and a diuretic. On examination, there was a Grade III/VI pansystolic murmur at the cardiac apex. Electrocardiogram showed atrial fibrillation. On cardiac catheterization, there was left atrial enlargement and significant calcific mitral stenosis and insufficiency with good left ventricular function.

A Starr-Edwards #2 mitral prosthesis was surgically inserted.

In the immediate postoperative period, the patient experienced a problem with fluid distribution and volume overloading of the pulmonary circuit, as determined by the pulmonary artery catheter. The data and treatment are outlined in Table 2.

Elevation of CVP over 13.0 cm. H_2O resulted in a precipitous increase of PAP; thus fluid intake was based on pressure changes in the pulmonary circuit. The patient's recovery was otherwise uneventful and he was discharged 10 days following operation.

Group II: The patient with postoperative cardiogenic shock provided a unique opportunity to evaluate the versatility of the catheter in diagnosing pulmonary circuit volume overload and in monitoring the progress of this volume overload to a treatment regimen of inotropic stimulation, pharmacologic peripheral vaso-dilatation, diuresis and transfusion.

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[†] Swan-Ganz flow directed right heart catheter. Edwards Laboratory, 17221 Red Hill Avenue, Santa Anna, California 92705.

TABLE 1

Type	Number of Patients
I. *Cardiac surgery*—valve replacement or coronary artery grafting	30
II. *Postoperative cardiogenic shock*	1
III. *Surgical endotoxic shock*	10
IV. *Pulmonary emboli*	12

Case 2. A 67-year-old woman with arteriosclerotic peripheral vascular disease and a myocardial infarction one year previous, underwent left aortofemoral bypass graft surgery. Twenty-four hours postoperatively, she developed crushing left anterior chest pain, diaphoresis and hypotension. Shortly, thereafter, respiratory failure occurred and she required intubation. Blood pressure was 80/0 mm. Hg.

An electrocardiogram showed depressed ST segments in V1-5. Arterial blood gases while on a Bennett respirator with 100% oxygen revealed a pH 7.18, Po_2 67 mm. Hg, Pco_2 44 mm. Hg, and HCO_3 8.7 mEq. Hematocrit was 27%. A pulmonary artery catheter was inserted, and the CVP was 22 mm. Hg, PAP 38/23 mm. Hg, and a pulmonary wedge pressure was 18 mm. Hg. A sample of mixed venous blood showed pH 7.04, Po_2 15 mm. Hg, Pco_2 60 mm. Hg, and HCO_3 15.

She was treated with bicarbonate, furosemide, bolus intravenous steroids (30 mg./Kg.) and transfused with packed red cells. Four hours later, blood pressure was 110/60 mm. Hg and urine output had increased to 120 cc./hr. The pulmonary wedge pressure had risen 25 mm. Hg and chest X-ray was compatible with pulmonary edema. Over the next 24 hours, the wedge pressure gradually increased to 50 mm. Hg despite continued therapy. The patient died on the fifth postoperative day due to irreversible left ventricular failure. Post-mortem examination demonstrated a massive acute and subacute myocardial infarction involving the interventricular septum and posterolateral left ventricular wall.

Group III: In the patients with endotoxic shock, the catheter was utilized to monitor fluid distributing capacity, and to procure samples of true mixed venous blood for determination of gas tensions, pH, lactate and oncotic pressure values. The following is a demonstrative case:

Case 3. A 64-year-old man was admitted to the hospital with gastrointestinal bleeding. He had undergone sub-total gastric resection 6 months previously for a bleeding duodenal ulcer. A marginal ulcer was diagnosed by X-ray on admission.

Twelve-hour gastric acid analysis was normal. He responded to conservative management.

TABLE 2

Time Post-op.	PAP	CVP	SP. GR. Urine	Treatment and Comments
Immed.	91 mm. Hg	19.5 cm. H_2O	1.020	Fluid restriction
1 hr.	71.5 mm. Hg	13.0 cm. H_2O	1.026	Diuretic
2 hrs.	58.0 mm. Hg	10.0 cm. H_2O	1.020	
8 hrs.	45.5 mm. Hg	13.0 cm. H_2O	1.016	Improved peripheral perfusion

pH throughout 7.37–7.44
Po_2 throughout 90–100 mm. Hg
8 hour fluid input 600 u. (75 cc./hr. D5W
8 hour fluid output 850 cc. urine and 200 cc. chest tube
PAP—pulmonary artery pressure
CVP—central venous pressure
SP. GR.—specific gravity

Several days after admission, massive bleeding recurred. He underwent near total gastrectomy, vagotomy, splenectomy, and a tube-feeding jejunostomy was performed.

Postoperatively, he developed respiratory failure with gram negative pneumonia, requiring tracheostomy. An *Escherichia coli* wound infection and an anastomotic leak developed which were treated with appropriate antibiotics. He was given Vivonex feedings via the jejunostomy tube.

His condition deteriorated on the fourteenth day postoperatively. He was obtunded and oliguric, temperature was 40°C, pulse 110/min. Blood pressure was 120/60 mm. Hg (normal was 180/95 mm. Hg) Blood cultures yielded *E. coli*. Serum creatinine was 2.1 mg./100 ml. Arterial blood gases showed pH 7.28, Po_2 94 mm. Hg, and Pco_2 51 mm. Hg; serum lactate was 23 mg./100 ml. and the oncotic pressure was 29 cm. H_2O.

A pulmonary artery catheter was inserted; the pulmonary pressure was 15/8 mm. Hg with a wedge pressure of 5 mm. Hg. Mixed venous Po_2 was 37 mm. Hg.

The osmolality of the tube feedings was decreased; by giving crystolloid and colloid fluids, the pulmonary artery pressure was maintained at 30–35/15–20 mm. Hg. He was digitalized and antibiotics were changed appropriately.

Within 36 hours, he was awake and responding. Urine output, blood pressure and pulse rate improved. Pulmonary artery pressure was 40/20 mm. Hg, and the mixed venous Po_2 was 55 mm. Hg. The arterial Po_2 was 110 mm. Hg. Serum lactate was normal and the oncotic pressure was 33 cm. H_2O. He continued to improve slowly and was discharged 2 months later with all fistulas healed and taking nourishment orally.

Group IV: The catheter was utilized in 12 cases of suspected pulmonary emboli which constituted a diagnostic problem. It was used in an effort to document elevated pulmonary artery pressure; the following case report exemplifies such a diagnostic problem:

Case 4. A 63-year-old man with a long history of chronic obstructive lung disease was admitted in acute respiratory failure. He had a 5-day history of increasing sputum production and increasing dyspnea and was given Penicillin and Tetracycline. Electrocardiogram revealed atrial flutter with a ventricular rate of 155/min.

The day after admission he had right calf pain and a trace of pitting edema. Pleuritic right lower chest pain with some dyspnea developed and arterial blood gas values deteriorated. Electrocardiogram changed to sinus rhythm with tall P waves in the right chest leads. An emergency lung scan revealed a filling defect in the right lower lobe. Heparin was begun.

His condition improved over the next 4 days. He then had an episode of pleuritic left anterior chest pain associated with nausea, emesis and orthopnea. Electrocardiogram reverted to atrial flutter with no other acute changes. Because of his precarious condition, it was impossible to perform a repeat scan. A CVP line was inserted and recorded 10 cm. H_2O. Because of the strong suspicion of recurrent pulmonary embolism, a pulmonary artery catheter was inserted and revealed a pulmonary artery pressure of 57/22 mm. Hg with a wedge pressure of 17 mm. Hg. Several hours

TABLE 3. *Complications*

Type	Number
Balloon rupture	3
Infection at cut-down site	1
Coiling in right ventricle	1
Run of premature ventricular contractions	1

later, another episode of pleuritic chest pain with hemoptysis occurred, the pulmonary artery pressure read 65/15 mm. Hg.

A vena caval ligation and tracheostomy were performed. The postoperative course was protracted, but the patient gradually recovered and was discharged from the intensive care facilities.

Discussion

The introduction of central venous pressure monitoring (CVP) was one of the first widely applicable attempts to detect myocardial dysfunction.

It is well recognized, however, that large changes can occur in left ventricular filling pressure and/or pulmonary artery pressure before such variations are manifested in the CVP.[1] Experimental and cardiac catheterization data have also shown that the pulmonary artery pressure, pulmonary wedge pressure and/or pulmonary "a wave" pressure are more reliable indicators of the changes in magnitude of the left ventricular filling pressure.[6,7,10,13]

Access to these vital data was not available to the critical care unit physician and surgeon until the Swan-Ganz flow directed catheter was introduced. Its clinical usefulness has already become apparent in patients with myocardial infarction.[13] Our results in 53 surgical patients also support its clinical efficacy.

The acid-base composition of the extracellular fluid compartment is more closely approximated by mixed venous blood than by arterial blood sampling. The P_{CO_2} of mixed venous blood is thought to reflect the prevailing CO_2 level of the peripheral CO_2 stores.[5] Clinical investigations have utilized mainly CVP blood samples and have yielded conflicting results.[8,16] Pulmonary artery catheterization allows access to true mixed venous blood samples. Canine experimentation indicates that mixed venous gas tensions represent an index of the adequacy of peripheral perfusion.[2,8,9] The experience with the ten cases of surgical sepsis would also tend to support this experimental conclusion.

Recurrent pulmonary emboli, particularly small frequent ones often present a clinical enigma, both diagnostically and therapeutically. As was experienced in the 12 cases of recurrent pulmonary emboli, the determination of the absolute level of pulmonary artery and pulmonary wedge pressure may be a valuable clinical aid in the diagnosis and management of such cases.

The presence of a catheter in the pulmonary artery greatly facilitates the determination of cardiac output and pulmonary venous resistance.[11]

The ease of utilization and the low complication rate are two additional points favoring the use of the catheter in critically ill patients[15] (Table 3). Only three complications were felt to be of clinical significance—infection, coiling of the catheter and premature contractions—giving an effective complication rate of 5.7%. This rate compares favorably in the 53 patients studied to that reported for CVP catheters in some series.[3]

Acknowledgment

The authors wish to express gratitude to Miss Joan Stoklosa, B.S., for her invaluable technical assistance.

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Pulmonary Microembolism after Blood Transfusions:

An Electron Microscopic Study

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DURING THE storage of blood for future transfusions, platelets and leucocytes become adhesive and form aggregates up to 200 micra or greater in diameter.[18,27] The extent of this aggregation can be demonstrated by the screen filtration pressure (SFP) method, which is a measure of the resistance of blood flow through a screen with multiple pores 20 micra[3].[18,29,37] Screen filtration pressure studies have shown that platelet-leucocyte aggregates develop maximally within a few hours after anticoagulation with heparin and in 1 to 7 days if anticoagulated in ACD solution.[18,21,22,36] After the first week of storage, the number of aggregates ranging in size from 10–164 micra may exceed 140,000/cc[3].[26] The design of commercially available infusion set filters tends to prevent the passage of particles 170 micra or larger.[23] It can be expected, therefore, that storage-formed platelet-leucocyte aggregates, 170 micra or smaller, enter the circulation during transfusion and are rapidly filtered from the blood by the lungs and peripheral capillary beds.[22,36] Such microemboli have been shown to obstruct and impair the function of various organs including the brain and lungs.[14,15,17,28,29] In fact, considerable evidence now exists implicating massive pulmonary microembolism from "debris" in stored blood as an etiologic factor in the development of the postoperative and post-traumatic pulmonary insufficiency syndrome.[15,22,23,30] In the present study, the effects of storage-formed platelet-leucocyte aggregates and other "debris" on canine pulmonary alveolar fine structure is examined. Since filtration of stored blood through Dacron wool has been shown by the SFP[27] and Coulter Counter[26] methods to remove these aggregates, an ultrastructural comparison is made between the lungs of dogs transfused through standard clot and Dacron wool filters.

Materials and Methods

Thirty adult mongrel dogs ranging in weight from 30 Kg. were anesthetized intravenously with pentobarbital sodium (25 mg./Kg.), and catheters for the infusion and removal of blood were inserted percutaneously into a jugular vein and a femoral artery. Twenty-six dogs, divided into four experimental groups, received a transfusion of stored blood equal to approximately 25% of each animal's normal blood volume by vein, while simultaneously, an equal volume of blood was removed from a femoral artery. In each instance, the transfusions took approximately 20 minutes. Blood was obtained from donor dogs, anticoagulated with acid citrate dextrose solution and treated in one of four ways for transfusion through either a standard clot or a Dacron wool filter.

In the first experimental group, the preserved blood was stored for 5 days at 4°C. This blood was then infused into four dogs through a standard clot filter and into another four through a Dacron filter.

In the second experimental group, the donor blood was treated with adenosine diphosphate at a concentration of 2.0 μg/cc, thoroughly mixed and immediately filtered through Dacron wool to remove aggregated platelets and leucocytes. This treatment has been shown

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to remove up to 95% of platelets and 75% of the leucocytes.[3,29] This blood was stored for 5 days at 4°C and subsequently infused into four dogs through a standard clot filter.

In the third experimental group, fresh citrated blood was centrifuged at 2000 rpm to a constant hematocrit, and the supernatant plasma and then the buffy coat were removed. After several washings in saline, the red cell mass was resuspended in plasma, and the buffy coat was resuspended in an equal volume of the same plasma. Both were stored for 5 days at 4°C. The red cells were then infused into four dogs and the buffy coat into three, both groups through a standard clot filter.

In the fourth experimental group, blood stored for 5 days at 4°C was centrifuged, separated, and then infused into seven animals as described in the third experimental group.

Just before transfusion, the units of stored blood were mixed to insure a homogeneity of the blood infused into each dog. The platelet enriched plasma was treated the same way for transfusion. Four control animals were treated the same as those transfused except that no blood was administered.

Following the experimental and control procedures, the dogs were sacrificed by an intravenous injection of sodium pentobarbital. The inferior vena cava was severed prior to expiration to reduce delivery of blood to the right heart. The chest was then opened to completely expose both lungs before antemortem gasping of the animal occurred.

To ascertain the diffuseness of pulmonary microembolism and alveolar fine structural alterations, tissue areas grossly free of hemorrhage were sampled from both the right and left upper and lower lobes. Specimen tissues for electron microscopic examination were initially fixed for one hour in 3% glutaraldehyde buffered to pH 7.4 with 0.1M sodium cacodylate containing 25 mg./100 ml. calcium chloride. They were postfixed in sodium cacodylate buffered 1% osmium tetroxide (pH 7.4), dehydrated in a graded series of ethanol, processed with propylene oxide and embedded in Epon 812. Thin sections were cut on a Porter Blum MT-2 microtome with diamond or glass knives. Tissue sections were stained with lead citrate and uranyl acetate to enhance contrast and examined with RCA EMU 3F and 4B electron microscopes. A random sample of 10 blocks from each lung was sectioned and examined to minimize the large sampling error inherent in electron microscopy.

Random samples of the Dacron wool filter, through which stored ACD anticoagulated blood had been filtered (group I) were washed free of non-adhering materials with physiological saline, dehydrated, made electrically conducting by coating in a vacuum chamber with a layer of evaporated gold/palladium mixture and examined for aggregate material with a Cambridge stereoscan S4 scanning electron microscope.

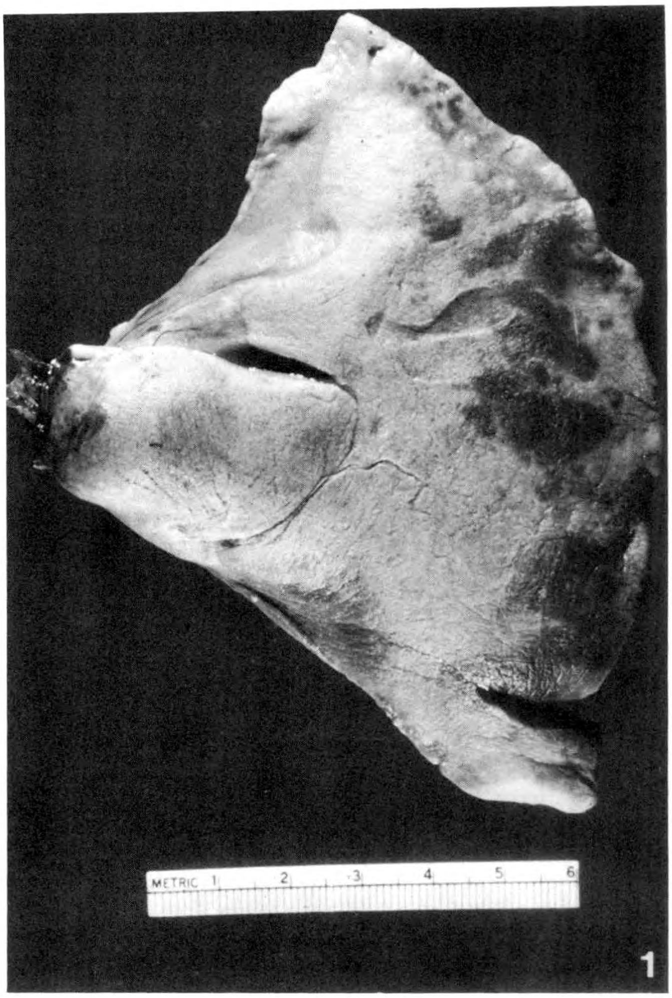

FIG. 1. Pulmonary hemorrhage following transfusions of 5-day old stored acid citrate dextrose anticoagulated blood filtered through a standard clot filter in an anesthetized dog.

Results

The lungs of those dogs in which stored acid citrate dextrose anticoagulated blood (group I) or platelet enriched plasma (groups III and IV) was transfused through a standard clot filter, grossly exhibited punctate and diffuse hemorrhages (Fig. 1). Histologically, many of the alveoli in the hemorrhagic areas were filled with red blood cells. When examined ultrastructurally, lung biopsies, which were taken from areas grossly free of hemorrhage, exhibited extensive occlusion of the pulmonary microcirculation by aggregates of disintegrating platelets and leucocytes and widespread degenerative changes in the cellular components of the interalveolar septum (Figs. 3, 4, 7 & 8). The most striking of these alterations occurred in the capillary endothelium and the alveolar type I lining cells (Figs. 4 & 8).

Changes in the capillary endothelium varied from

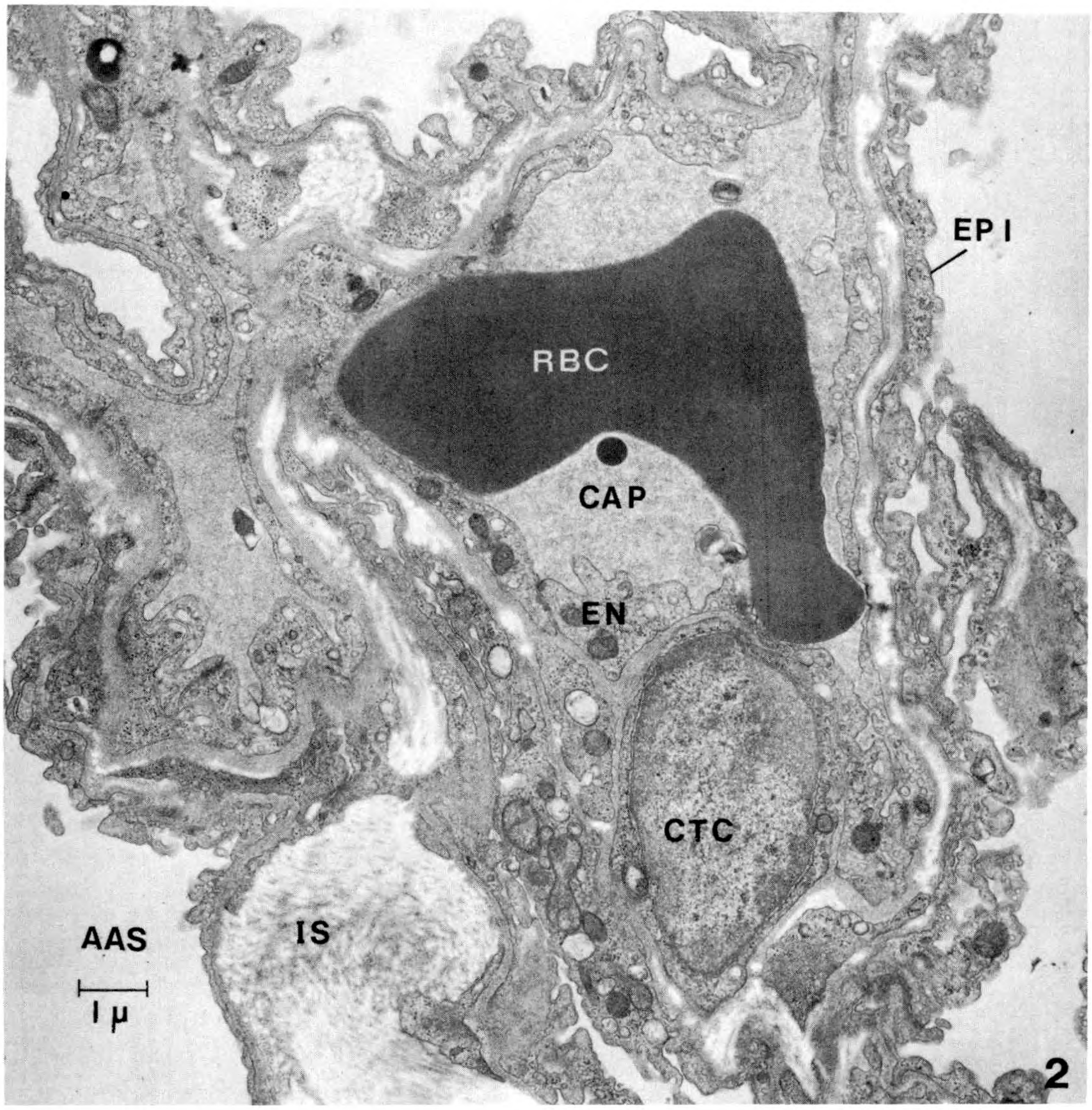

FIG. 2. Control biopsy demonstrating normal pulmonary alveoli. The air spaces (AAS) are lined by attenuated type I alveolar epithelial cells (EPI), which are separated from endothelial (EN) lined capillaries (CAP) by a connective tissue space (IS) containing an occasional connective tissue cell (CTC) and collagen fibrils. Red blood cells (RBC).

marked swelling and disruption and rarefaction of cytoplasmic and nuclear matrices (Fig. 8) to focal blistering and lysis of surface membranes (Fig. 3). In every instance, the lumina of the vessels contained conglomerants of membrane-bound cytoplasmic fragments, coarsely clumped granular material, and numerous dense lysosomal granules. Degenerative alterations were more severe in those obstructed capillaries in which lysosomal granules from disintegrating leucocytes were in close association with the endothelium. In these regions, capillary endothelial cells were either fuzzy with indistinct surface membranes or completely detached from the underlying capillary wall (Fig. 4). This resulted in areas exhibiting intraluminal remnants of desquamated endothelial cells and surface areas denuded of endothelium with basal lamina in direct contact with the capillary lumen. Similar degenerative changes were seen in the type I alveolar epithelial cells (Figs. 3 & 8). These cells were generally swollen and their cytoplasm and nuclei rarefied. Similarly the surface membranes of these cells frequently appeared fuzzy and were occasionally ruptured, resulting in a discontinuity of the alveolar epithelium (Fig. 8). The type II alveolar epithelial cells appeared unchanged except for a slight increase in cytoplasmic vacuolization and blunting of surface microvilli (Fig. 7). Despite the presence of disintegrating platelets and leucocytes, no fibrin was seen in the vascular spaces. In those areas where cellular change occurred, protein exudates were observed in the interstitial as well as in the alveolar air spaces (Figs. 4 & 8). Greater amounts of this protein exudate were observed in the alveolar air spaces of those dogs transfused with platelet enriched plasma which had been prepared after 5 days of storage (Fig. 8). Other than this, very little qualitative

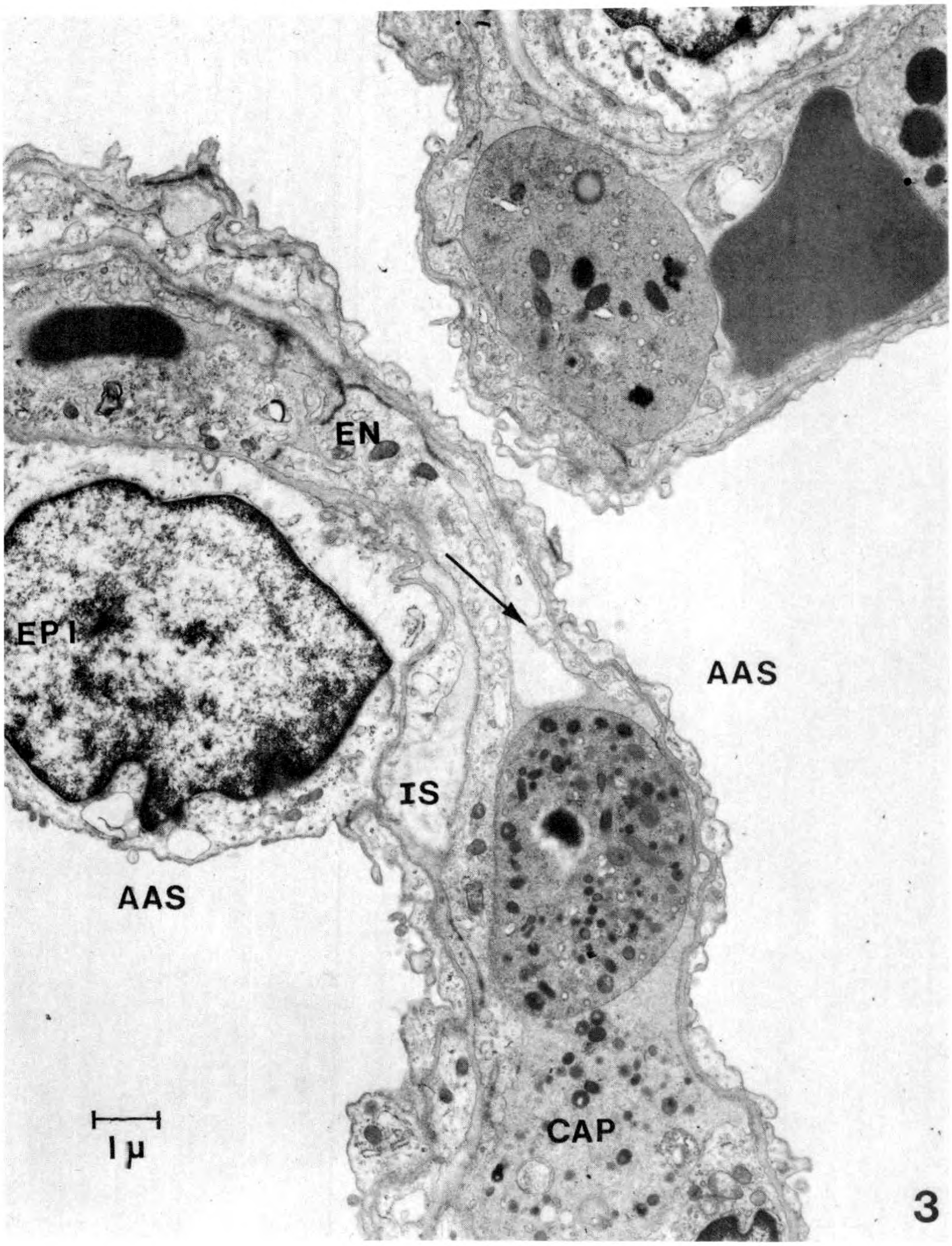

FIG. 3. Lung biopsy from a dog transfused with 5-day old stored acid citrate dextrose anticoagulated blood infused through a standard clot filter. The capillaries (CAP) are filled with fragments of disintegrated platelets and leucocytes. The alveolar type I epithelium (EPI) exhibits cytoplasmic and nuclear rarefaction. The endothelium (EN) also shows cytoplasmic rarefraction and focal rupture in its luminal surface plasma membrane (arrow). Alveolar air space (AAS).

difference in the extent of pulmonary fine structural change was observed between dogs receiving transfusions of stored whole blood and platelet enriched plasma through a standard clot filter.

The lungs of those animals which received transfusions of stored preserved blood through a Dacron wool filter and those in which the blood was pretreated with adenosine diphosphate and filtered through Dacron wool to remove the platelet-leucocyte aggregates before being transfused through a standard clot filter, were both grossly and microscopically free of pathologic alterations (Figs. 5 & 6). Similarly, no changes were observed in the lungs of those dogs which received transfusions of washed red blood cells through a standard clot filter.

When examined with the scanning electron microscope, the Dacron wool, through which stored ACD anticoagulated blood had been filtered (group I), revealed the presence of large amounts of adhesive debris en-

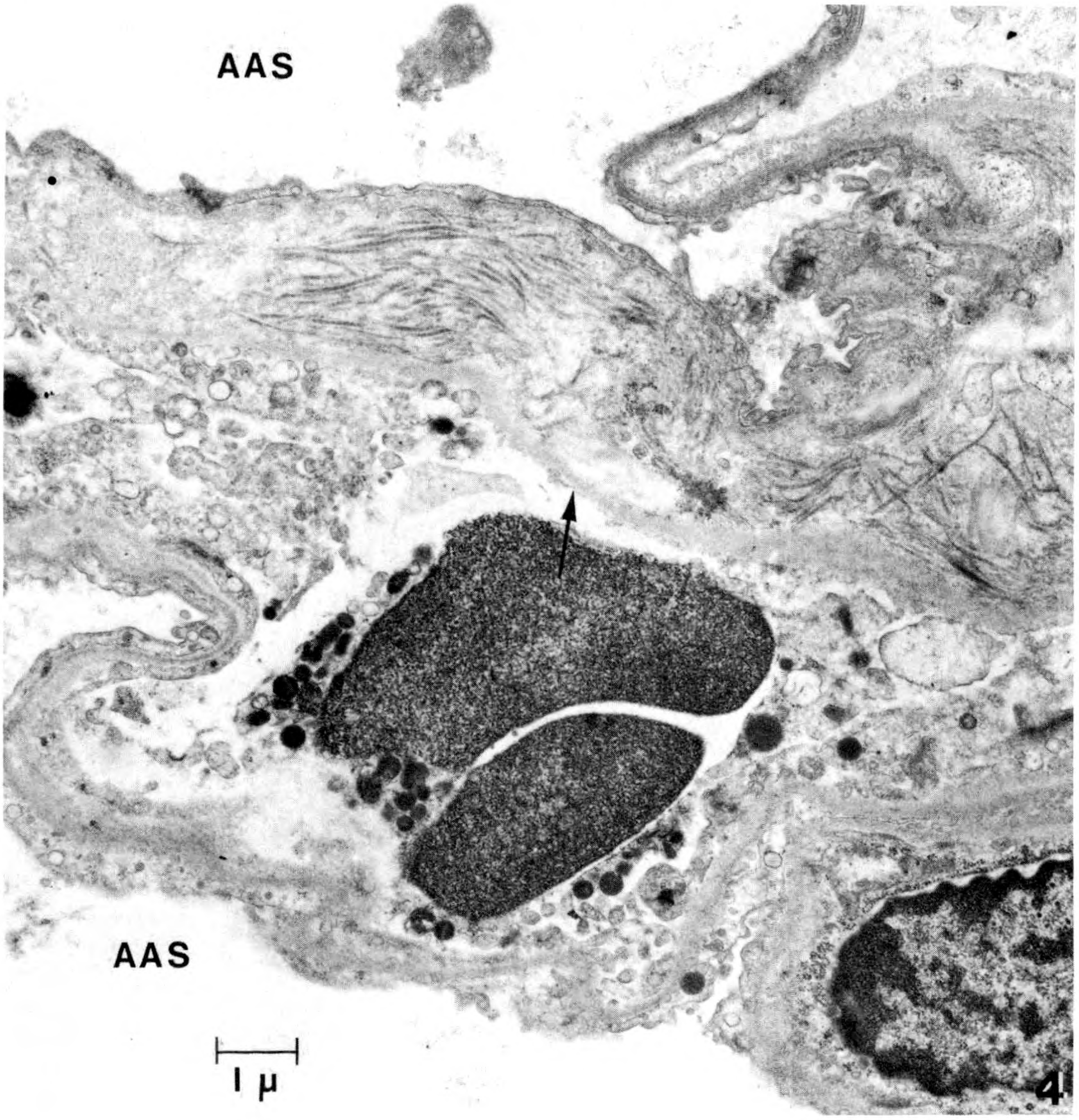

FIG. 4. Lung biopsy from a dog transfused with 5-day old stored acid citrate dextrose anticoagulated blood infused through a standard clot filter. Cytoplasmic remnants of desquamated endothelium and a disintegrated leucocyte fill the lumen of a pulmonary capillary. The endothelial lining of the vessel is indistinct and focally discontinuous, thus exposing the underling basal lamina (arrow) to the vessel lumen. Traces of plasma exudate are seen in the interstitial and alveolar air space (AAS).

tangled or trapped in the dense mesh of Dacron fibers (Figs. 9 & 10). This material included sheets and aggregates of platelets and leucocytes.

Discussion

The present study not only provides confirming morphological evidence of significant pulmonary vascular obstruction by platelet-leucocyte aggregates, but also demonstrates severe degenerative alterations in the cellular components of the interalveolar septum. Both of these effects were the result of massive transfusions of stored, preserved blood. The absence of microvascular occlusion and alveolar damage in animals which received stored blood filtered through Dacron wool strongly suggests that adhesive platelets and leucocytes and their aggregates are intimately involved in the formation of these lesions. This observation is also supported by the presence of identical lesions in those animals infused wtih platelet-enriched plasma, and by the absence such change following infusions of washed red cells. Examination of the electron micrographs did not reveal significant amounts of amorphous or unrecognizable debris, nor the presence of fat emboli in the microvasculature of the lungs.

The presence of platelet-leucocyte aggregates in stored, preserved blood, attended by an elevation of SFP has been observed microscopically in blood smears,[27] and quantitated to size and number.[23,26] Within one week of storage, the number of aggregates ranging in size from 10–164 microns may exceed 70 million per unit of blood.[26] These aggregates, which are not removed by standard clot filters, appear histologically similar to those plugging the microcirculation of lungs and other organs after

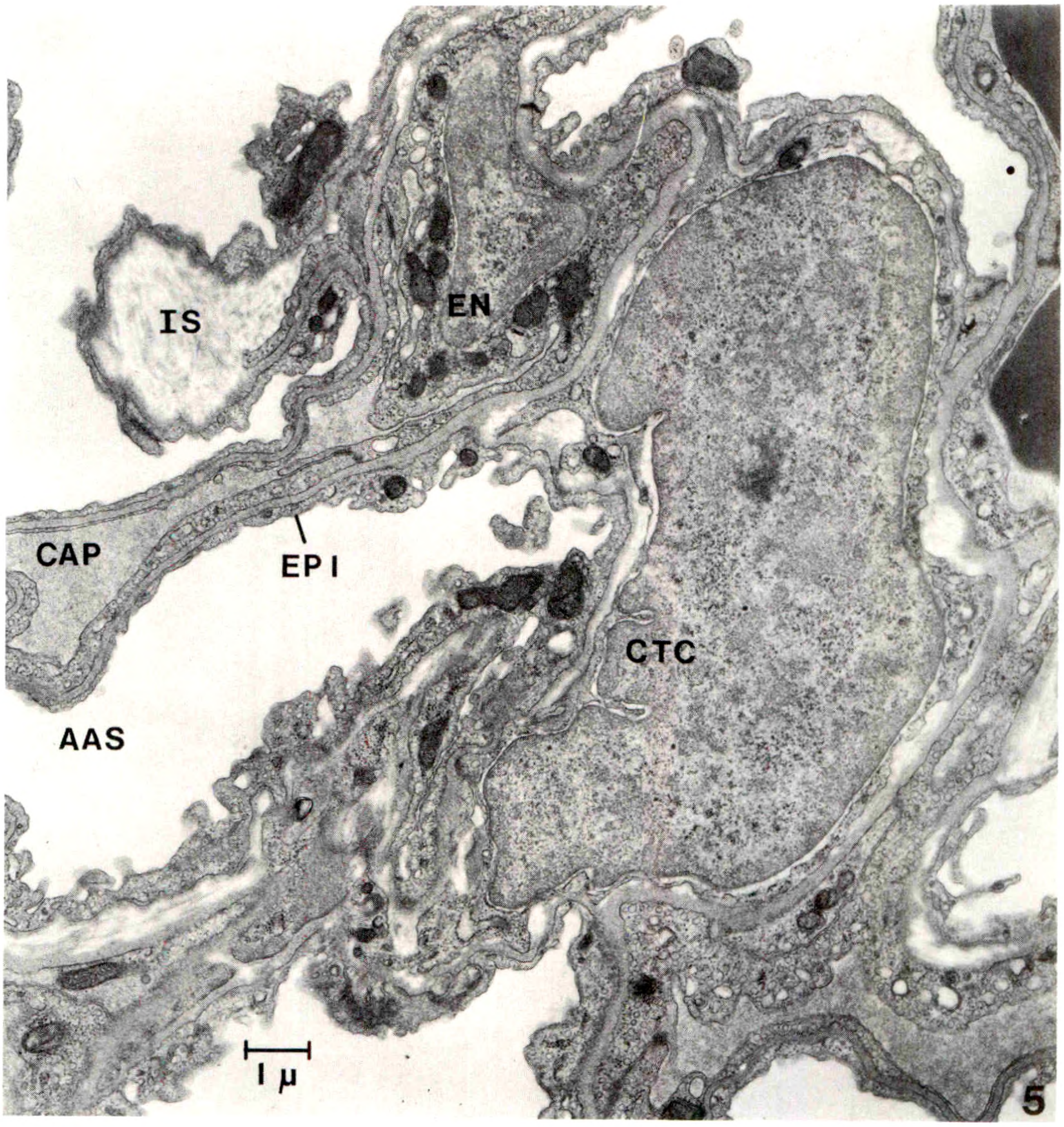

FIG. 5. Lung biopsy from a dog transfused with 5-day old stored acid citrate dextrose anticoagulated blood infused through a Dacron wool filter. Fine structure reveals normal alveolar lining cells (EPI), interstitial elements (IS) and capillary endothelial cells (EN). No platelet-leucocyte emboli are present in the pulmonary vessels (CAP). Alveolar air space (AAS), connective tissue cell (CTC).

large transfusions, pump oxygenator procedures and hemorrhagic and nonhemorrhagic shock.[2,4,12,15,17,22,23,24,27,30,36] The degenerative fine structural lesions observed in the cellular components of the interalveolar septum in the present study are similar to those described in canine lungs following experimental, regional and systemic shock.[5,10,12,19] In these studies, various degrees of pulmonary microembolism associated with severe degenerative changes, such as swelling, vacuolation, disruption and lysis of capillary endothelial and type I and II alveolar epithelial cells were reported. Similar endothelial changes have been described in pulmonary arterioles of isolated dog lungs after 60 minutes of perfusion with fresh homologous blood anticoagulated with acid citrate dextrose solution.[38] Clinical findings currently suggest that the development of the post-traumatic pulmonary insufficiency syndrome seen in combat casualties in Vietnam is more closely related to the volume of transfused blood than to the actual trauma or shock.[22] Results of the current study suggest that it may be possible to avoid these changes, in part or totally, by removal of platelet-leucocyte aggregates. In this study, it has been shown that this can be accomplished easily by filtering blood through Dacron wool. A more laborious method of accomplishing the same result is to centrifuge and wash the red cells several times with saline prior to resuspension and transfusion. Hill *et al.*,[13] using Dacron filtration during cardiopulmonary bypass procedures, recently reported a decrease of 65% in the mortality rate following open-heart surgery and a decrease of 95% in the number of nonfat (platelet-leucocyte) cerebral emboli in patients examined postmortem. The removal of

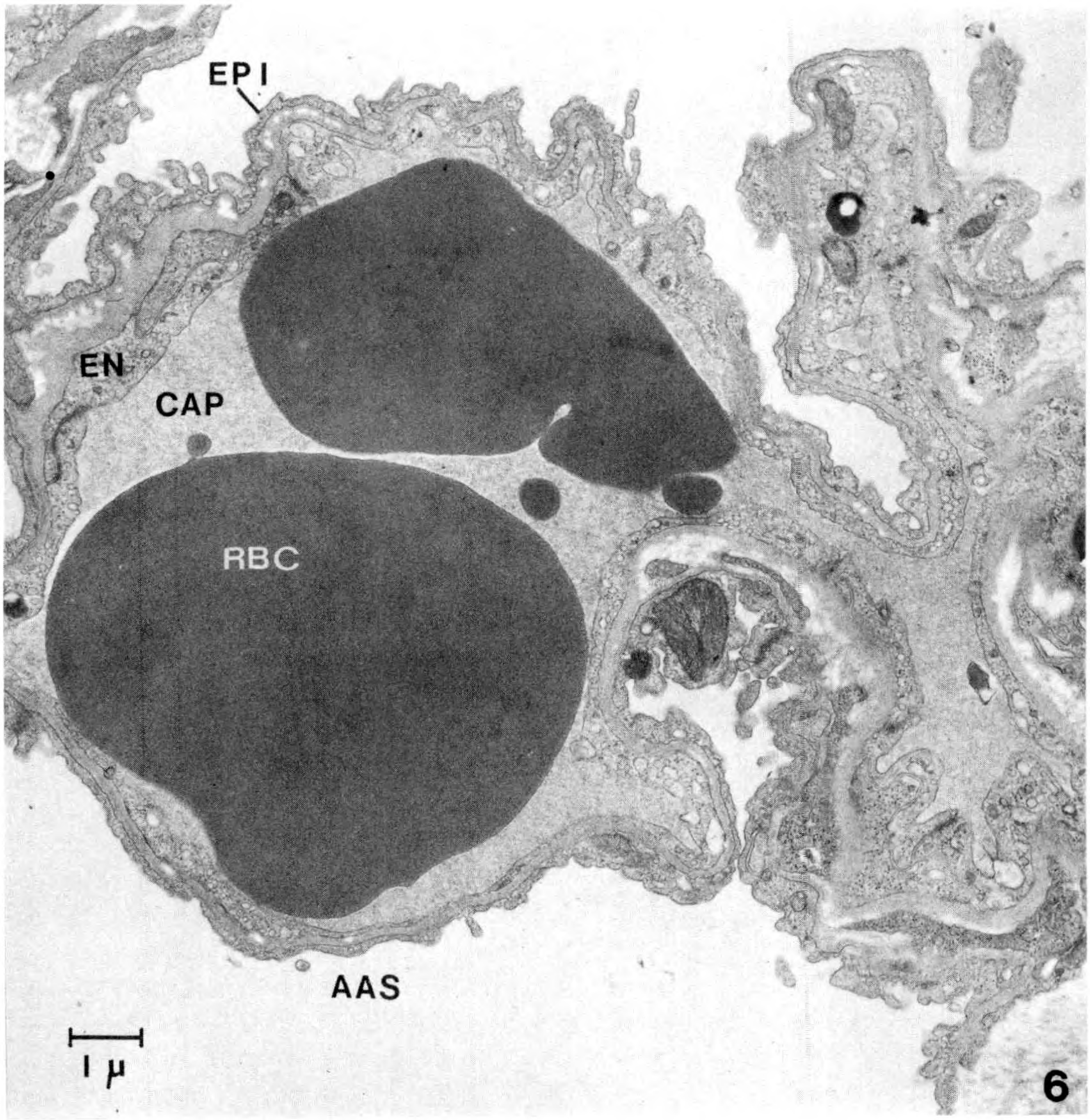

FIG. 6. Lung biopsy from a dog transfused with acid citrate dextrose anticoagulated blood treated with adenosine diphosphate (2.0 µg/cc), filtered through Dacron wool and stored for 5 days before being infused through a standard clot filter. As in Fig. 5, no microvacular occlusion or degenerative changes are seen in the alveolar fine structure. Alveolar air space (AAS), capillary lumen (CAP), endothelium (EN), type I alveolar epithelium (EPI), red blood cell (RBC).

storage-formed aggregates by Dacron wool filtration, thus providing a more suitable perfusate, has been well documented.[1,11,25,31,32,35] The SFP of stored human ACD anticoagulated blood pretreated with ADP and/or serotonin is greatly elevated due to increase in platelet and leucocyte adhesiveness and aggregation. Filtration of such blood through Dacron wool removes these aggregates and returns the SFP to normal.[29] Similarly, increases in the SFP of dog blood during experimental hypotension were shown to decrease to or below normal if the animal's blood was perfused through Dacron.[35] The potent filtering action of the pulmonary vascular bed in the removal of gross and microscopic aggregates has also been demonstrated physiologically. When the amount of stored blood transfused into an intact dog exceeded 25% of his normal blood volume, an arterial-alveolar air P_{CO_2} difference developed, attended by pulmonary artery hypertension.[30] Since the latter does not necessarily develop before 65% of the pulmonary microcirculation is occluded,[16] it is evident that significantly large areas of the pulmonary circulation must have been obstructed by aggregated materials following transfusions. This hypothesis is confirmed by the present ultrastructural observations.

A second cause of platelet-leucocyte aggregates may have been due to mixing donor blood with the recipient dog's normal blood during transfusion ("mixing phenomenon").[3] Single, or a few aggregated and adhesive platelets and leucocytes may form nuclei to which the dog's normal platelets and leucocytes adhere. Further adhesiveness and aggregation are probably also promoted and potentiated by the biogenic amine (serotonin) and by adenosine diphosphate[7,29,33,34] released to the blood by cell destruction. The release of serotonin

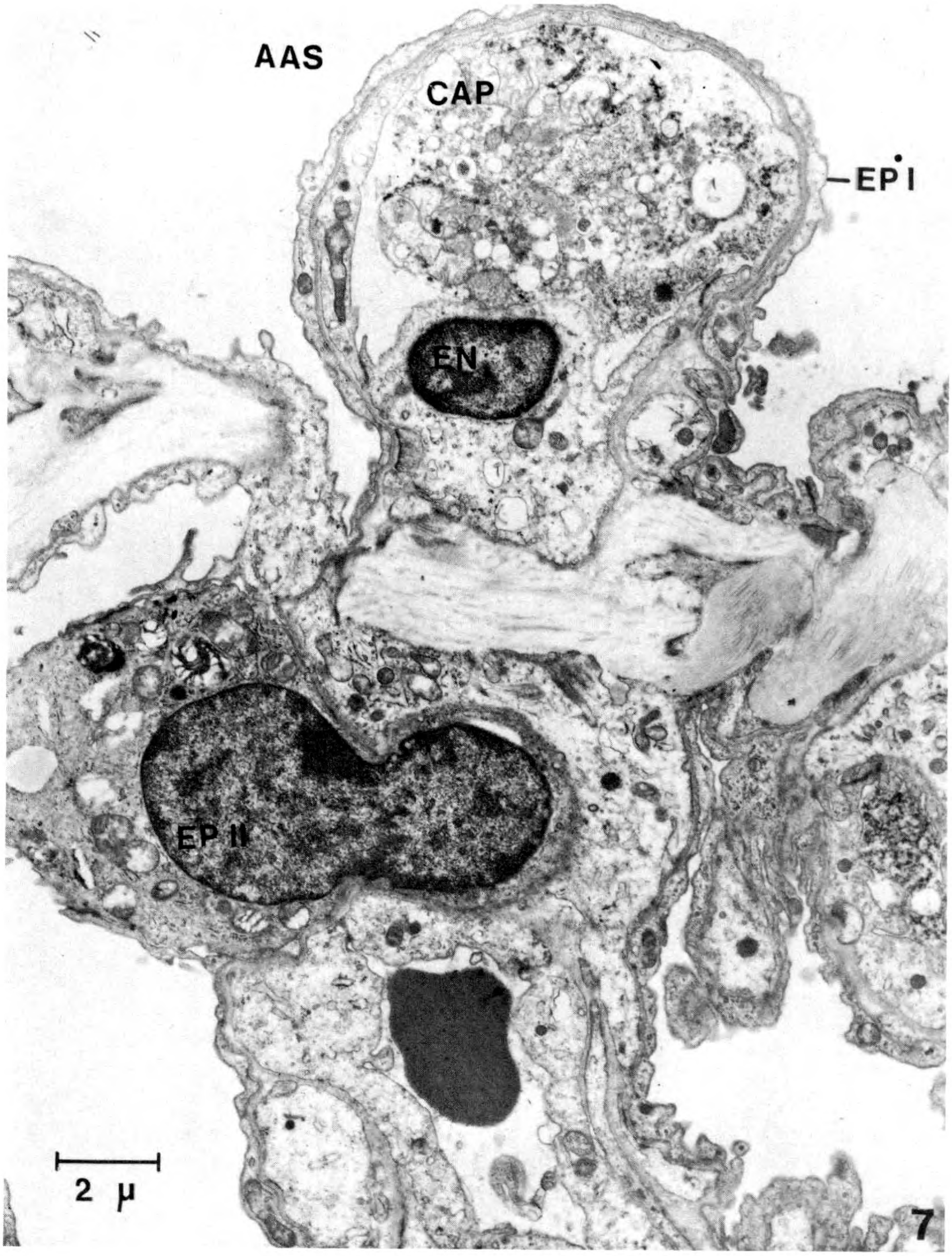

FIG. 7. Lung biopsy from a dog transfused with platelet enriched plasma, which was immediately separated from the red cell mass, stored 5 days and infused through a standard clot filter. The capillary endothelium (EN) and alveolar type I epithelium (EPI) exhibit degenerative changes. The capillary lumen (CAP) contains conglomerants of membrane-bound cytoplasmic fragments and clumps of granular material. No appreciable change is observed in the type II alveolar epithelial cell (EPII). Alveolar air space (AAS).

as well as histamine lead to further loss of vascular integrity by causing an increase in the permeability of the microcirculation.[20] The presence of intraluminal conglomerates of leucocytes and/or clusters of small dense granules in areas with extensive degenerative lesions, suggests that the disintegration of leucocytes and subsequent release of their lysosomes effect a lysis of endothelial cell plasma membranes. The specific granules or leucocytes, which have been identified as lysosomes on the basis of their morphological composition, enzymatic content and functional activities,[8,9] have been shown to cause damage to cells in the Shwartzman and Arthus reactions.[39] Both an increase in permeability and focal discontinuities in the endothelial lining of the microcirculation would account for the exudation of protein-laden fluid into the alveolar interstitium. This exudate may mechanically cause further damage by lifting the capillary endothelium and alveolar type I epithelial

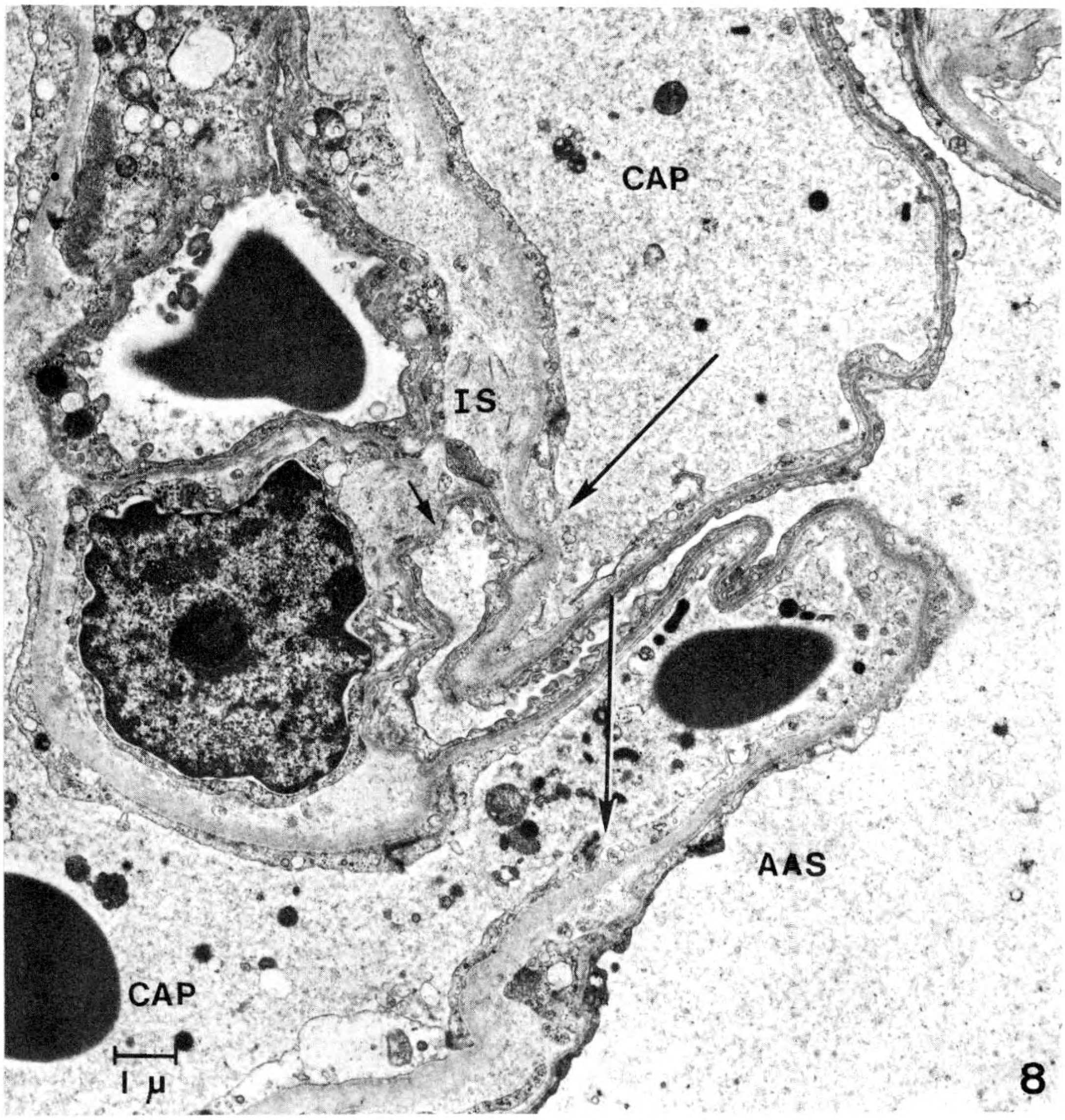

FIG. 8. Lung biopsy from a dog transfused with platelet enriched plasma which was stored 5 days and then separated from the red cell mass and infused through a standard clot filter. The endothelial lining of the capillaries (CAP) which contain numerous dense lysosomal granules is focally swollen with indistinct and often discontinuous plasma membranes (large arrows). Similar degenerative changes including a discontinuity ocur in the type I alveolar epithelial cells (small arrow). As a result of such cellular disruption, large accumulations of granular protein-laden exudates are observed in the interstitial (IS) and alveolar air spaces (AAS).

cells in blister fashion. Subsequently, rupture and/or detachment from underlying basal lamina would occur. With the loss of alveolar epithelial integrity, protein exudates may freely flow into the alveolar air spaces. Such extravasation may lead to the inhibition of surfactant activity[6] and certainly serves as an osmotic force favoring further transudation of fluid.

Summary

The findings of this study demonstrate that transfusions of stored ACD anticoagulated blood or of plasma enriched with platelets cause not only extensive occlusion of the pulmonary microcirculation by aggregates of disintegrating platelets and leucocytes, but widespread degenerative lesions in the capillary endothelial and type I alveolar epithelial lining cells. Transfusing identical blood through Dacron wool, which removed adhesive platelets, leucocytes and their aggregates, or removal of platelets and leucocytes from blood by other means prior to transfusion, did not produce microvascular obstruction and the formation of degenerative changes in the pulmonary fine structure.

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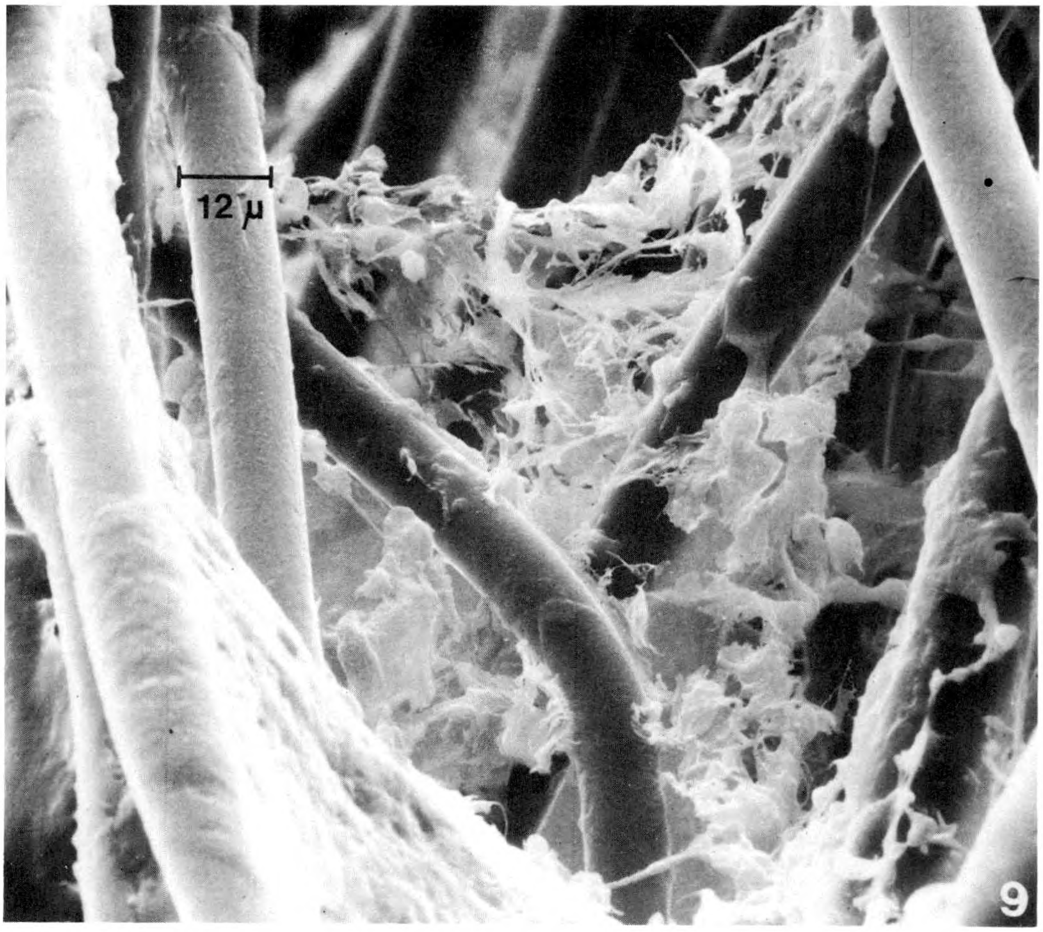

FIG. 9. Scanning electron micrographs demonstrating adhesive material including platelets and leucocytes and their aggregates filtered from 5-day old stored acid citrate dextrose anticoagulated canine blood.

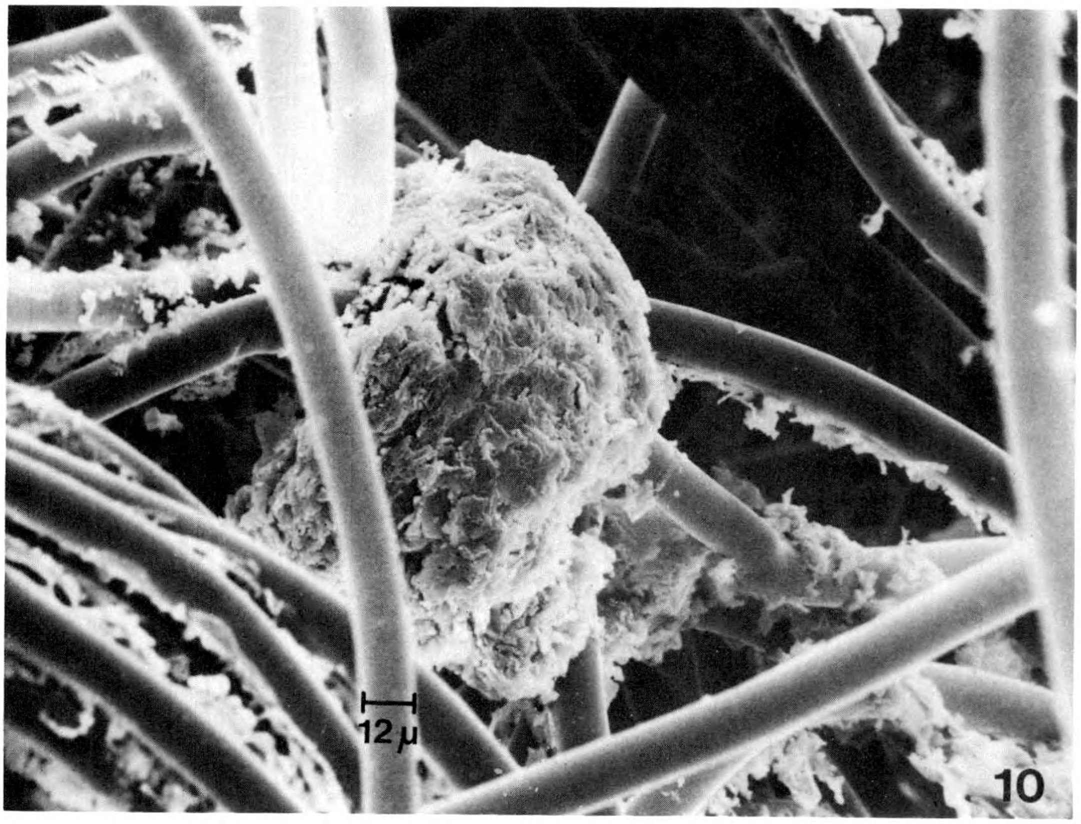

FIG. 10. See legend for Figure 9.

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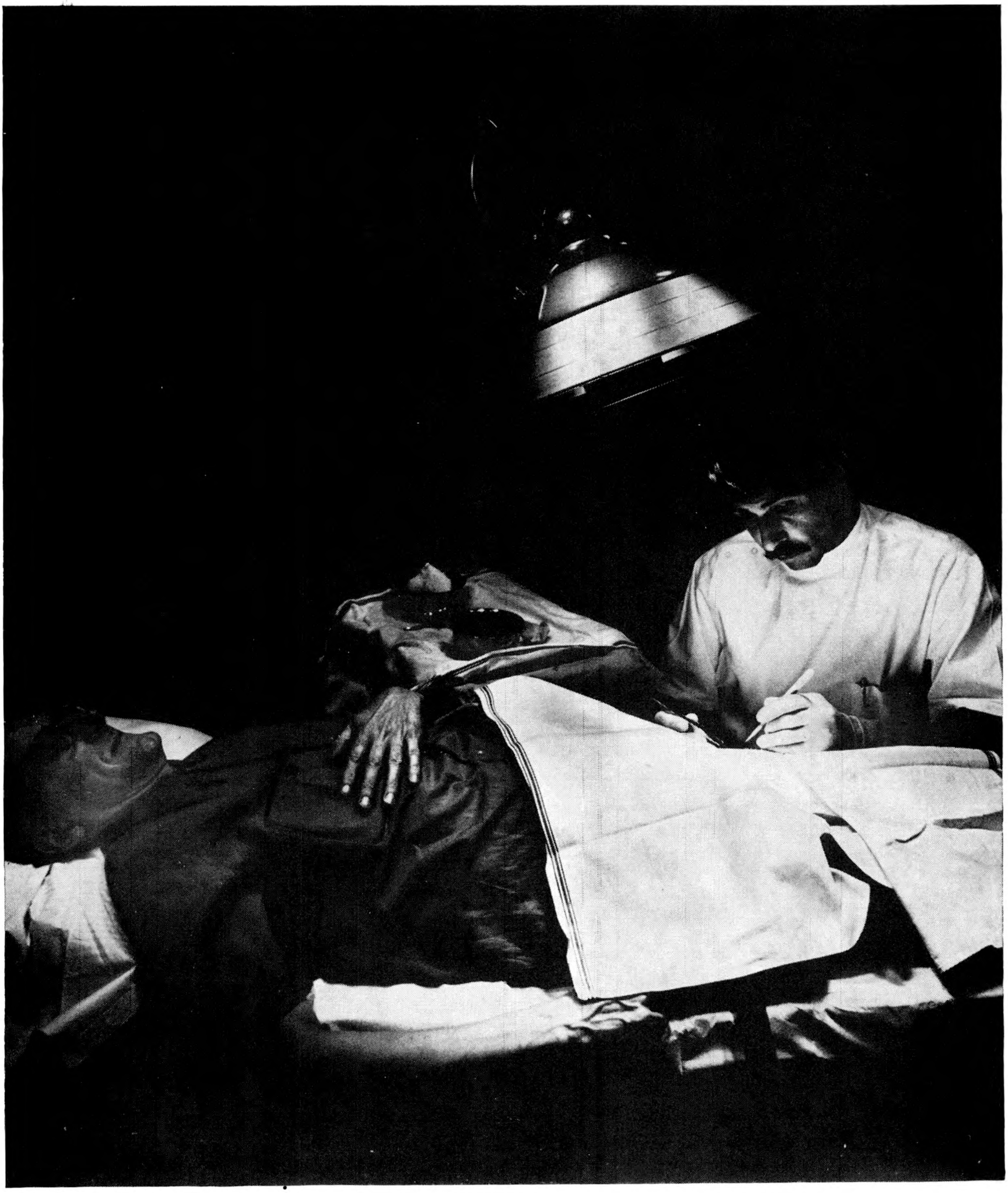
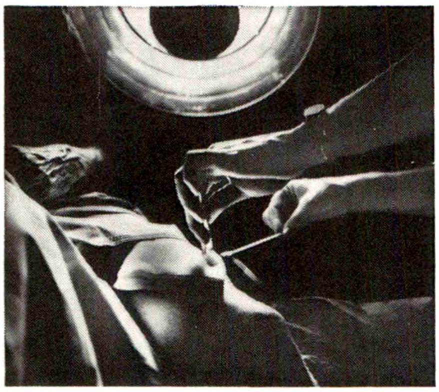
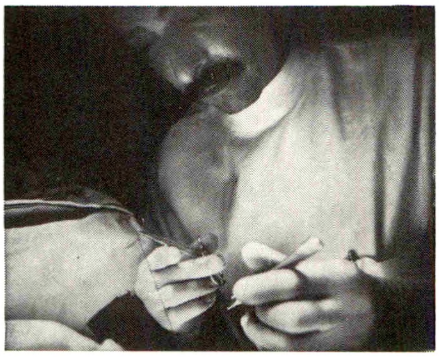
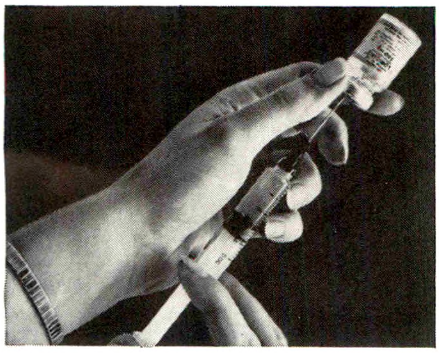


Loridine® I.M. (cephaloridine) 500-mg. ampoule

therapy worthy of consideration







Traumatic wound infections often require the rapid and effective action that Loridine I.M. can provide when they are due to susceptible organisms.

Loridine is active in vitro against many pathogens that may cause skin and soft-tissue infections, including susceptible strains of staphylococci, *Escherichia coli,* and streptococci, and is also effective in the presence of mixed infections.†

One dose of Loridine provides measurable serum levels of antibacterial activity up to twelve hours.

These are a few of many reasons why Loridine provides therapy worthy of consideration.

†Many strains of enterococci are relatively resistant. Some strains of staphylococci are resistant. *Pseudomonas* organisms are resistant, as are most indole-producing *Proteus* species and motile *Enterobacter* species.

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Before Administration of Loridine

1. Determine renal status before *initiating* therapy.

2. In patients with renal impairment, reduced dosage should be employed. Other antibiotic therapy should be considered if impairment is due to acute tubular necrosis.

3. As with other antibiotics, appropriate specimens for culture and susceptibility testing should be obtained.

4. Use cautiously with other potentially nephrotoxic antibiotics (e.g., gentamicin, kanamycin, colistin, and polymyxin B), in penicillin-allergic patients, and in those receiving potent diuretics, such as furosemide or ethacrynic acid.

During Administration of Loridine

1. Because of potential nephrotoxicity, daily dosages above 4 Gm. are not recommended for patients with normal renal function. The usual range for adults is 1.5 to 3 Gm. daily. In patients with renal impairment, recommendations in the package literature should be followed for *maintenance dosage* after a loading dose of 0.5 to 1 Gm. If an endogenous creatinine clearance is considered more desirable than available BUN or serum creatinine concentrations for establishing the maintenance dosage, the initial loading dose may be given and results of that test obtained during the ensuing six or eight hours. If renal function improves during therapy, readjustment of dosage may be desirable.

2. Maintain proper hydration.

3. Monitor renal status. Renal impairment may be indicated by the appearance of urinary casts, proteinuria, oliguria, a rising BUN or serum creatinine, or a decreasing creatinine clearance or urine/plasma creatinine ratio.

4. If impaired renal function develops or worsens during therapy, discontinue use.

Please turn page for prescribing information.

Loridine® I.M. (cephaloridine)

Because of nephrotoxicity (e.g., tubular necrosis) of cephaloridine in dosages above 4 Gm. daily (see Warnings and Adverse Reactions), recommended doses should not be exceeded. Renal status of the patient should be determined prior to initiation of therapy. Patients with known or suspected impairment of renal function should be under close clinical observation for changes in renal function or be hospitalized, and reduced dosage should be employed. If impaired renal function develops during therapy, cephaloridine should be discontinued.

Actions: *Human Pharmacology*—Peak blood levels of 7 and 14 mcg. per ml. respectively were obtained in one-half to one hour following intramuscular doses of 250 and 500 mg. in humans. Measurable levels of cephaloridine persisted for longer than twelve hours.

Loridine is excreted unchanged largely by glomerular filtration. Doses of 250 and 500 mg. produced very high antibacterial concentrations in the urine, in some instances approaching 1,000 mcg. per ml.

Its nucleus and degradation products differ from those of penicillin. However, some patients who are allergic to penicillin or to other cephalosporins may also be allergic to Loridine.

Microbiology—The in-vitro bactericidal action of Loridine results from inhibition of cell-wall synthesis. It is not bound significantly to plasma protein.

Loridine is active against the following organisms in vitro:

- Beta-hemolytic and other streptococci (many strains of enterococci, e.g., *Streptococcus faecalis,* are relatively resistant)
- Staphylococci, both coagulase-positive and coagulase-negative (some strains of staphylococci are resistant to cephaloridine)
- Pneumococci
- Gonococci
- *Hemophilus influenzae*
- *Escherichia coli* and other coliform bacteria
- *Klebsiella*
- *Proteus mirabilis*

Loridine is active against *Treponema pallidum* in animal studies.

All tested strains of group A streptococci, pneumococci, and penicillin-G-susceptible staphylococci are susceptible to Loridine. However, some strains of penicillinase-producing staphylococci are resistant in vitro to concentrations of Loridine that can be achieved in the serum. The majority of strains of *H. influenzae, Pr. mirabilis, Esch. coli,* and *Klebsiella* are also susceptible in vitro.

Pseudomonas organisms are resistant to Loridine, as are most indole-producing *Proteus* species and motile *Enterobacter* species.

Indications: Loridine is indicated in the treatment of serious infections of the respiratory tract, genito-urinary tract, bones and joints, bloodstream, soft tissue, and skin due to susceptible strains of the organisms listed above. It is also indicated for therapy of early syphilis when penicillin may be contraindicated. (*See* Warnings in regard to cross-sensitivity with penicillin.) It is indicated in the treatment of gonorrhea when penicillin is not considered the drug of choice.

Appropriate culture and susceptibility studies should be performed. If the susceptibility tests show that the causative organism is resistant to Loridine, other appropriate antibiotic therapy should be instituted.

Contraindications: Loridine is contraindicated in those persons who have shown hypersensitivity to it or other cephalosporins.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS. INSTANCES OF PATIENTS WHO HAVE HAD SEVERE REACTIONS TO BOTH DRUGS, INCLUDING DEATH FROM ANAPHYLAXIS, HAVE BEEN REPORTED.

Impairment of renal function during treatment may be indicated by the appearance of casts in the urine, proteinuria, falling urinary output, a rising BUN or serum creatinine, or a decreasing creatinine clearance or urine/plasma creatinine ratio.

Cephaloridine should be given cautiously when used with other antibiotics having nephrotoxic potential, e.g., gentamicin, kanamycin, polymyxin B, and colistin.

The results of experimental studies in animals suggest that the concurrent use of potent diuretics, such as furosemide or ethacrynic acid, may increase the risk of renal toxicity.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions: In the case of infections due to beta-hemolytic streptococci, antibiotic therapy should be continued for at least ten days.

In the therapy of gonorrhea, patients in whom there is reason to suspect concomitant syphilis should have dark-field examinations of all suspect lesions before treatment and monthly serologic tests for a minimum of three months.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Superinfections may develop with organisms not in the spectrum of Loridine, particularly *Pseudomonas*. These can be recognized by clinical observation and by means of appropriate cultures. If they occur, proper therapeutic measures should be taken.

Since safety for use in premature infants and in infants under one month of age has not been established, administration of cephaloridine to these patients is not recommended.

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest® tablets but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: *Hypersensitivity*—Maculopapular and erythematous rashes, urticaria, and anaphylaxis have been reported. Drug fever and eosinophilia also have been noted. Hypersensitivity reactions are more likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—Neutropenia and leukopenia have been reported. Some individuals have developed positive direct Coombs tests during therapy.

Liver—Transient elevations of transaminase and alkaline phosphatase levels have been noted. The significance of these findings is uncertain.

Renal—Severe, acute renal failure, in some cases terminating in death, has occurred in a small number of patients receiving Loridine. The possibility of this complication seems to be greater in seriously ill patients given more than recommended doses. Acute tubular necrosis has been noted in affected patients coming to autopsy.

Local Reactions—Pain on I.M. injection of Loridine is rare, and phlebitis on I.V. injection occurs infrequently.

Other—Nausea and vomiting have been reported.

Administration and Dosage: Ampoules should be protected from light. Extemporaneous mixtures of Loridine with other antibiotics are not recommended.

Loridine should be dissolved in either Sodium Chloride Injection or Sterile Water for Injection (*see* the package literature for dilution table).

Intramuscular Injection—Loridine is usually injected into a large muscle mass, for example, the gluteal region or the lateral aspect of the thigh.

The usual adult dosage for many infections of moderate severity is 500 mg. to 1 Gm. three times a day at equally spaced intervals. Milder and more susceptible infections have been treated with 250 to 500 mg. given two or three times a day. More severe infections may be treated with 500 mg. to 1 Gm. four times a day.

A single 2-Gm. dose is recommended for the treatment of acute gonorrhea.

Early syphilis may be treated with 500 mg. to 1 Gm. daily for ten to fourteen days.

Although some clinical experience with high doses for life-threatening conditions has been reported, it has been shown that excessive dosages (above 4 Gm. daily) may cause serious nephrotoxic reactions. For this reason, Keflin® (sodium cephalothin, Lilly) may be preferred when doses larger than 4 Gm. daily are considered for life-threatening situations. If more than 2 Gm. of cephaloridine is injected daily, the patient should be under close clinical observation for changes in renal function or be hospitalized. In addition, reduced dosage should be employed in patients with known or suspected renal impairment (*see* the package literature).

In children, a daily total of 30 to 50 mg. per Kg. (15 to 25 mg. per pound) of body weight, given in divided doses, has been found effective for mild to moderately severe infections. A daily total of 100 mg. per Kg. (50 mg. per pound) of body weight (not to exceed recommended adult doses) may be needed for very severe infections. Since safety for use in premature infants and in infants under one month of age has not been established, the use of cephaloridine in these patients is not recommended.

In both adults and children, failures have appeared to be related more closely to insusceptibility of the organism or poor general condition of the patient than to inadequate dosage.

Intravenous Injection—In the presence of extremely serious infections (such as bacteremia) or when any infection seems overwhelming, intravenous administration may be indicated.

Total daily dosages are the same as with intramuscular injection. For very susceptible organisms, 500 mg. to 1.5 Gm. per day may suffice; for less susceptible organisms and for serious infections, 2 to 4 Gm. per day may be needed.

How Supplied: Ampoules Loridine® (cephaloridine, Lilly), as follows:

250 mg., 5-ml. size, rubber-stoppered, in packages of 50 (No. 771) accompanied by six 20-ml. ampoules of Bacteriostatic Sodium Chloride Injection, U.S.P.

500 mg., 5-ml. size, rubber-stoppered, in packages of 1 (No. 722); also available in packages of 50 (No. 772) accompanied by six 20-ml. ampoules of Bacteriostatic Sodium Chloride Injection, U.S.P.

1 Gm., 10-ml. size, rubber-stoppered, in packages of 1 (No. 723); also available in packages of 25 (No. 773) accompanied by four 20-ml. ampoules of Bacteriostatic Sodium Chloride Injection, U.S.P.

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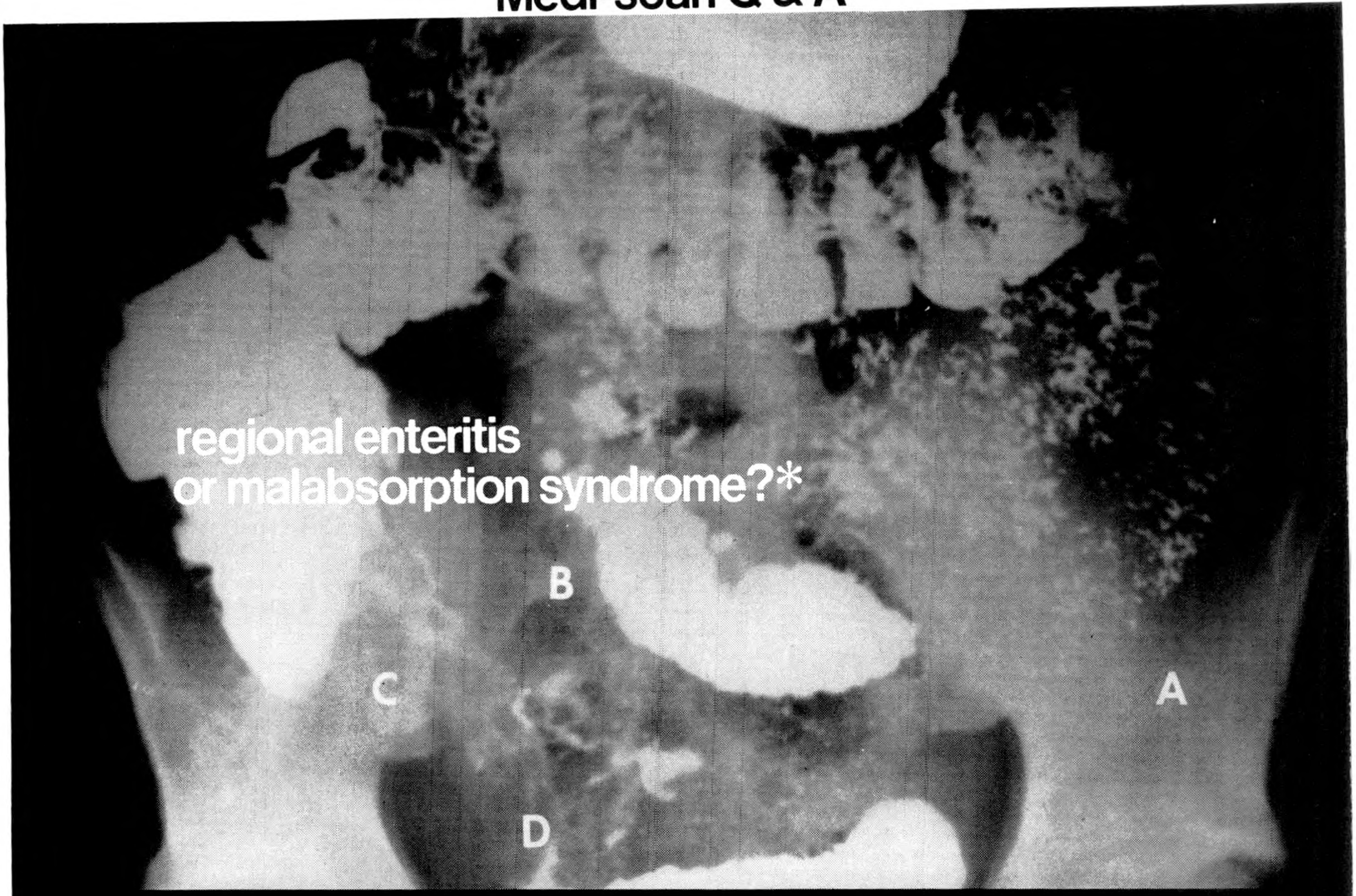

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*** Regional enteritis is revealed in this x-ray. The diagnostic signs include scattering (A), "moulage sign" or claylike clumps (B), destruction of the terminal ileal mucosa (C), and fistulation adjoining the terminal ileum (D). There is no thickening of the bowel mucosa or fistulation in malabsorption syndrome.**

Elase

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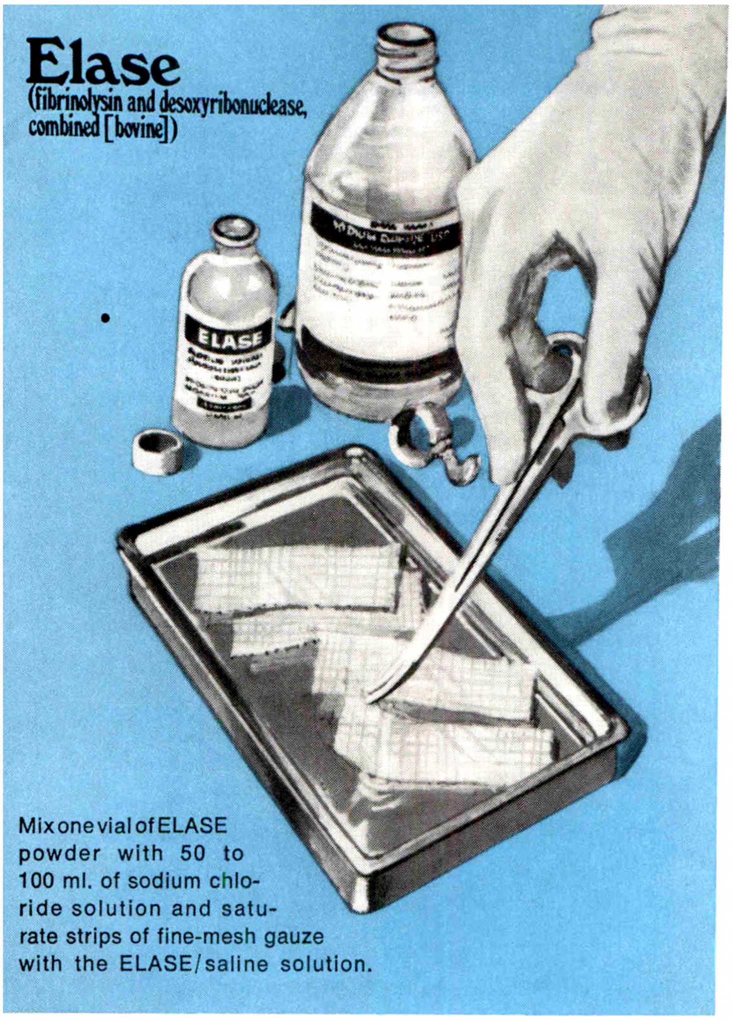
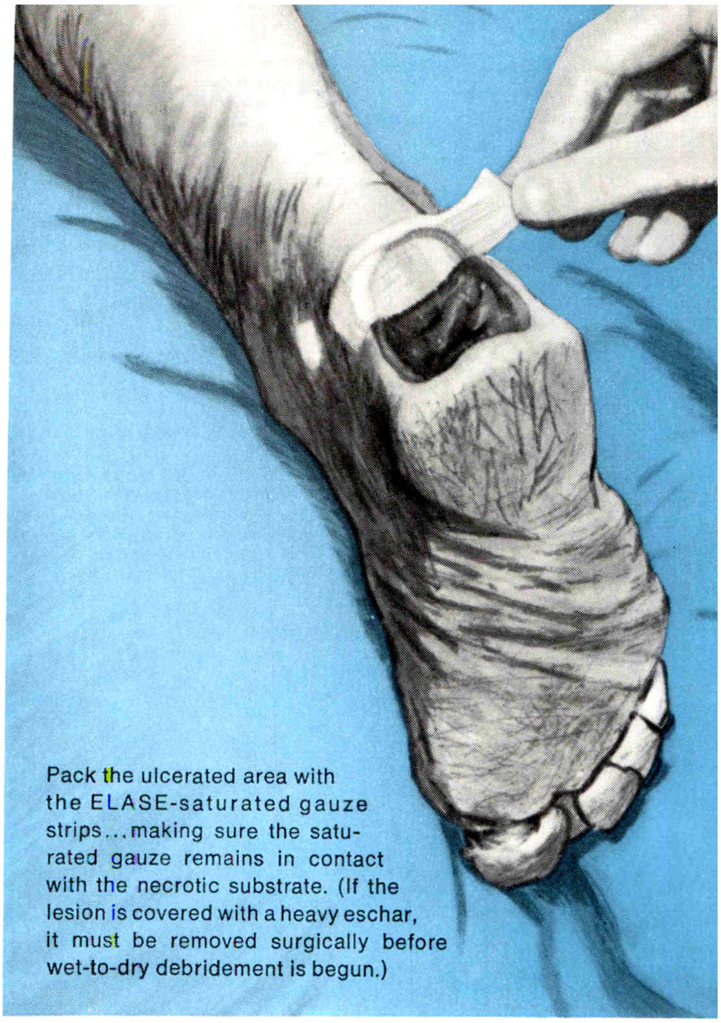
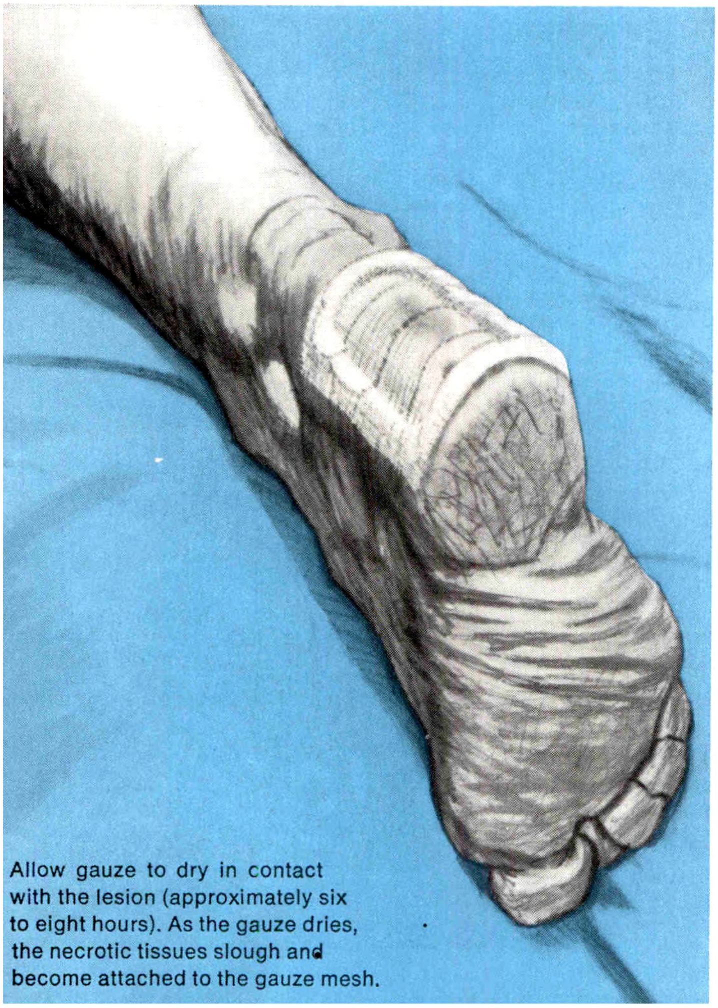


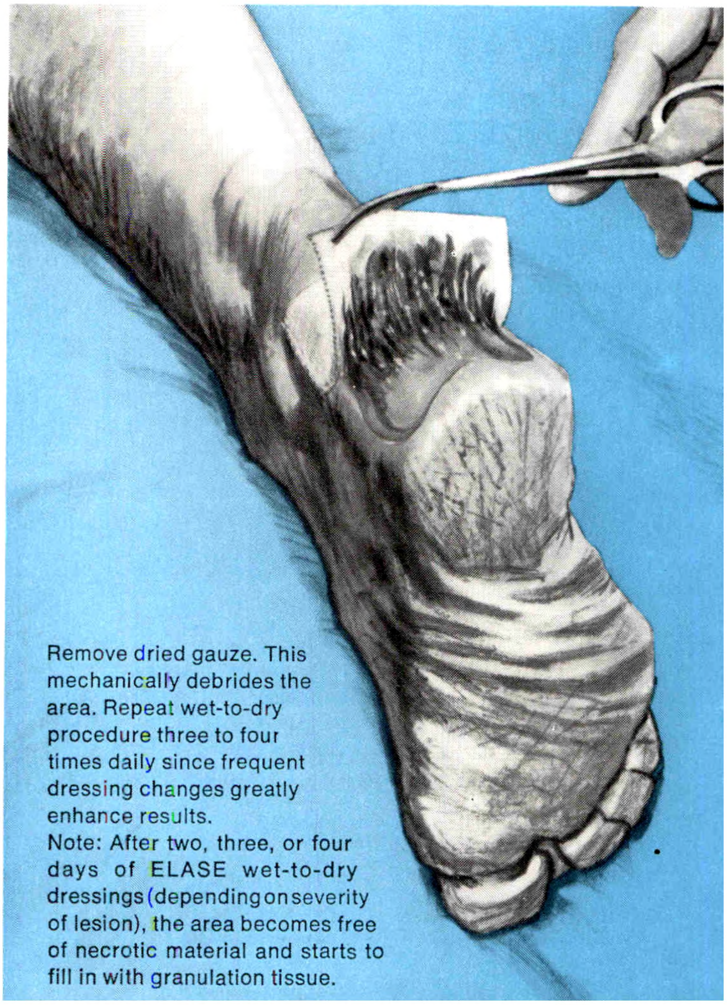
Mix one vial of ELASE powder with 50 to 100 ml. of sodium chloride solution and saturate strips of fine-mesh gauze with the ELASE/saline solution.



Pack the ulcerated area with the ELASE-saturated gauze strips . . . making sure the saturated gauze remains in contact with the necrotic substrate. (If the lesion is covered with a heavy eschar, it must be removed surgically before wet-to-dry debridement is begun.)



Allow gauze to dry in contact with the lesion (approximately six to eight hours). As the gauze dries, the necrotic tissues slough and become attached to the gauze mesh.



Remove dried gauze. This mechanically debrides the area. Repeat wet-to-dry procedure three to four times daily since frequent dressing changes greatly enhance results.

Note: After two, three, or four days of ELASE wet-to-dry dressings (depending on severity of lesion), the area becomes free of necrotic material and starts to fill in with granulation tissue.

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(fibrinolysin and desoxyribonuclease, combined [bovine])

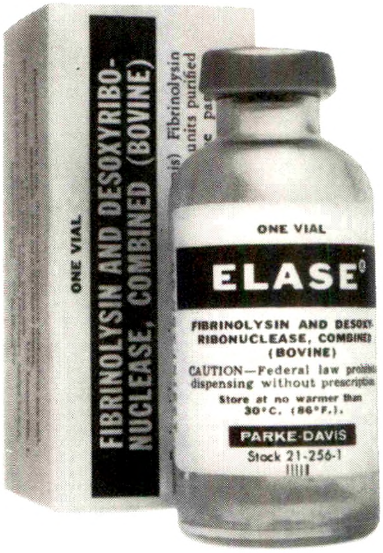
INDICATIONS: Elase is indicated for topical debridement in general surgical wounds, ulcerative lesions, burns, circumcision and episiotomy, and in cervicitis and vaginitis. Elase is used as an irrigating agent in infected wounds, otorhinolaryngologic wounds, and superficial hematomas (except when the hematoma is adjacent to or within adipose tissue).

CONTRAINDICATIONS: Elase is contraindicated in individuals with a history of hypersensitivity reactions to any of the components. Elase is not recommended for parenteral use since the bovine fibrinolysin may be antigenic.

PRECAUTIONS: The usual precautions against allergic reactions should be observed, particularly in persons with a history of sensitivity to materials of bovine origin or to mercury compounds.
To be maximally effective, Elase solutions must be freshly prepared before use. The loss in activity is reduced by refrigeration; however, even when stored in a refrigerator, the solution should not be used 24 hours or more after reconstitution.

ADVERSE REACTIONS: Side effects attributable to the enzymes have not been a problem at the dose and for the indications recommended. With higher concentrations, local hyperemia may be a side effect.

HOW SUPPLIED: Elase (powder) is supplied dried in 30-cc. rubber-diaphragm-capped vials containing 25 units (Loomis) of fibrinolysin and 15,000 units (modified Christensen method) of desoxyribonuclease with 0.1 mg. thimerosal (mercury derivative).
Elase Ointment is supplied in 30-Gm. tubes containing 30 units (Loomis) of fibrinolysin and 20,000 units of desoxyribonuclease with 0.12 mg. thimerosal and in 10-Gm. tubes containing 10 units of fibrinolysin and 6,666 units of desoxyribonuclease with 0.04 mg. thimerosal.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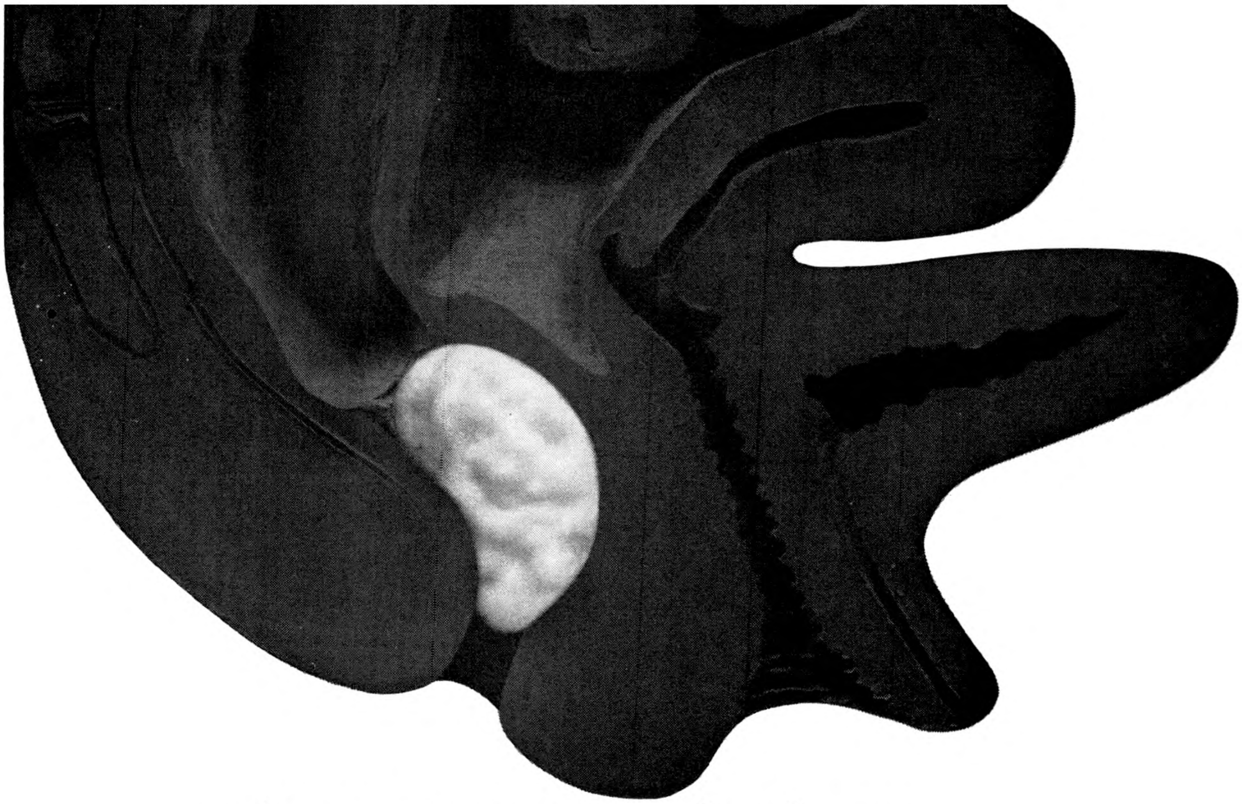

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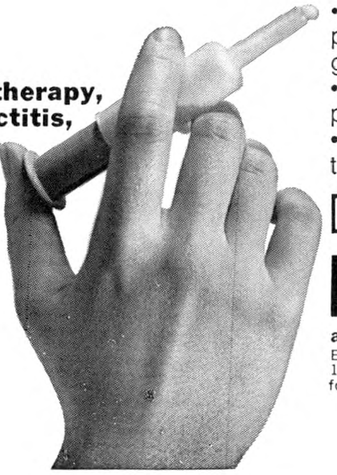

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Dosage: One applicatorful two or three times daily and after each bowel evacuation. Perianally, apply as needed.
How Supplied: In aerosol container providing 15 Gms. of medication (approx. 25 applications) with special rectal applicator and patient instructions.
References: 1. Bernstein, I.: *Surg. Dig. 4*:23, Jan. 1969. **2.** Sladek, W. R.: Scientific exhibit presented at 69th Annual Meeting of American Proctologic Society, Hollywood, Fla., April 12-16, 1970. **3.** Sladek, W. R.: *Amer. J. Clin. Res. 1*:33, Jan.-Feb. 1970. **4.** O'Brien, J. R.: *Surg. Dig. 4*:27, April 1969. **5.** Miller, H.: *Amer. J. Proctol. 18*:59, Feb. 1967. **6.** Lieberman, W.: *Amer. J. Proctol. 20*:134, April 1969.

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REVIEW

Effects of Saline and Colloid Resuscitation on Renal Function

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IN A RECENT STUDY carried out in Vietnam,[2] the effectiveness of resuscitation with 5% albumin and whole blood was compared with Ringer's lactate plus whole blood. It was reported that those patients treated with the 5% albumin did not fare as well clinically, required twice as much blood, and made half as much urine as those casualties resuscitated with the Ringer's lactate. This suggests that renal function is less effectively restored in those patients treated with the 5% albumin. Our objective was to compare renal function in baboons subjected to hemorrhagic shock and resuscitated with either 5% albumin in Ringer's lactate, or with Ringer's lactate.

Methods and Material

A. *Preliminary Procedures*

Thirteen adult baboons weighing 12.6 to 20.3 Kg. were the test animals. One week prior to study, siliconized, heparin filled, polyethylene catheters (PE-240) were surgically implanted into the left renal vein, and the free end ligated and buried subcutaneously.[12] On the day of the study, the renal vein catheter was reexposed, aspirated of heparin, and filled with heparinized saline. Polyethylene catheters (PE-240) were introduced into the aortic arch and suprarenal vena cava via the femoral vessels. Vascular pressures were monitored with one pair of arterial and caval catheters. Hemorrhage was accomplished with the remaining arterial catheter and fluids were infused via the remaining caval catheter. A suprapubic bladder catheter was inserted, as well as a uretheral catheter for complete bladder drainage. The animal was then loosely restrained in the prone position, with his chest protected by axillary supports. At the time of the study, the animal had recovered from the effects of the minor surgery and was completely awake.

B. *Experimental Model* (Fig. 1)

The study was divided into four periods: *Baseline*, *Shock*, *Resuscitation*, and *Recovery*.

Baseline: During the 4-hour baseline period, the animal received an intravenous infusion of normal saline at a rate of 10 cc./Kg./hr., producing a constant basal urine output. A priming dose of PAH (40 mg./Kg.) and Inulin (75 mg./Kg.) was given 75 minutes prior to hemorrhage, followed by a constant infusion of 0.75% PAH and 1.5% Inulin in saline at 4 cc./Kg./hr. At 60 and 75 minutes after priming, arterial and renal vein samples, as well as 15-minute urine collections were obtained. All infusions were then discontinued and hemorrhage begun.

Shock: Hemorrhagic shock was induced by a 15-minute gradual hemorrhage, reducing the mean arterial pressure (MAP) to 50 mm. Hg. This MAP was maintained for 60 minutes by adjusting the volume in a blood reservoir containing 67.5 cc. of ACD solution. Urine output was measured every 15 minutes.

Resuscitation: Resuscitation was carried out over a 90-minute period. During the first 30 minutes (T-1), the test solution was given, followed by a 15-minute rest period. The shed red cells were returned during the next 15 minutes (T-2), followed by a 30-minute infusion of the test fluid if required (T-3). During T-1

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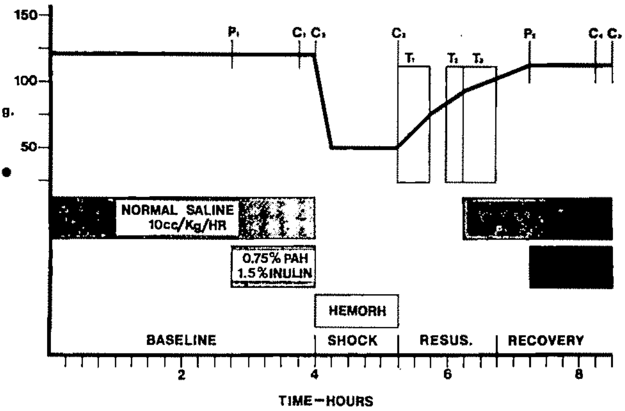

FIG. 1. Diagrammatic Scheme of experimental model. Priming with 40 mg./Kg. of PAH and 75 mg./Kg. Inulin at points P_1 and P_2 during baseline and recovery periods respectively. Continuous infusion with 0.75% PAH and 1.5% Inulin in saline at 4 cc./Kg./hr. from priming point until arterial, renal vein, and urine samples collected at points C_1 and C_2 during baseline, and points C_4 and C_5 during recovery. Hemorrhage (Hemorh) was 75 minutes. End of shock blood samples collected at point C_3. Resuscitation partitioned into three periods, T_1, T_2, and T_3 with test fluid given during T_1 and T_3, and shed packed red cells returned during T_2. The test fluid, chosen by random selection, was either 5% albumin in Ringer's lactate or Ringer's lactate alone.

and T-3, the test fluid, chosen by random selection, was either 5% albumin in Ringer's lactate ($n = 6$) or Ringer's lactate solution ($n = 7$). Infusion with the test fluid was carried out until either baseline MAP was restored or until baseline central venous pressure (CVP) was exceeded by 7 mm. Hg, at which time the infusion was halted. Infusion was resumed only if both MAP was below basal values *and* CVP did not exceed basal values by more than 4 mm. Hg. During the last 30 minutes of resuscitation, the 10 cc./Kg./hr. normal saline infusion was resumed.

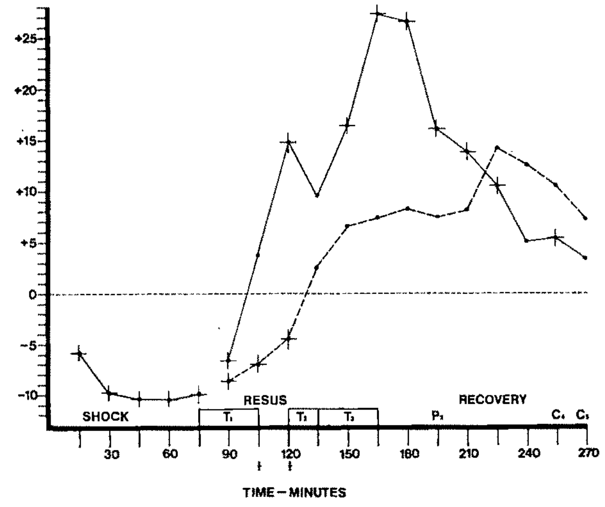

FIG. 2. Changes in urinary output during shock and after resuscitation. Baseline urine output was 10.2 ± 1.5 cc./Kg./hr. Shown is mean change from baseline at 15-minute intervals during the entire shock, resuscitation and recovery periods. The changes shown during shock are the pooled changes for all animals. During resuscitation and recovery, the changes in the Ringer's lactate group are denoted by the solid line, and the changes in the albumin group are denoted by the broken line. A significant change from basal values is denoted by ✚ and a significant difference between groups is denoted by ✛.

Recovery: Thirty minutes after the end of the resuscitation period, estimation of the PAH and Inulin clearances was begun with an identical priming dose and continuous infusion as given during the basal period. Arterial and renal vein samples, as well as 15-minute urine collections, were again obtained 60 and 75 minutes after priming. The study was then terminated by sacrificing the animals. During the entire resuscitation and recovery period, urine outputs were measured every 15 minutes.

C. *Renal Clearance Determinations*[1,5]

Plasma and urine concentrations of Inulin and PAH were determined with standard color development and spectrophotometric technics, using a Coleman Jr. Spectrophotometer. The extraction ratio of PAH (E-PAH) was calculated as:

$$\%\,\text{E-PAH} = \frac{A - V_r}{A} \cdot 100$$

where A is the arterial concentration and V_r is the renal vein concentration of PAH. Renal clearance of PAH (C-PAH) was calculated in the standard fashion:

$$\text{C-PAH} = \frac{U \cdot V}{P}$$

where U is the urinary concentration of PAH, P is the arterial plasma concentration of PAH and V is the urinary volume in cc/min. Corrected renal blood flow (RBF/E) was then calculated as:

$$\text{RBF/E} = \text{C-PAH/E-PAH/1.0-Hct.}$$

where Hct. is the hematocrit in decimal form.

Glomerular filtration rate (GFR) was determined by Inulin clearance:

$$\text{GFR} = \frac{U \cdot V}{P}$$

where U is the urinary concentration of Inulin, V is the urinary volume is cc./min., and P is the arterial plasma concentration of Inulin.

Plasma and urinary osmolarities were determined with a Precision Osmette, osmometer. Osmolar clearance was determined using the standard clearance formular above, substituting plasma and urine osmolarities. Free water clearance (FWC) was then determined by the formula:

$$\text{FWC} = \text{Urine volume} - \text{osmolar clearance.}^*$$

RBF/E and GFR are expressed in cc./Kg./min. Free water clearance and osmolar clearance are expressed in cc./Kg./hr.

Serum and urine sodium and potassium concentrations were determined with a flame photometer (IL. 143). The sodium and potassium clearances were calculated using the standard clearance formula. The tubular reabsorption (TR) of sodium and potassium were then calculated by the formula:

$$\%\mathrm{TR(X)} = \frac{\text{C-In} - \text{C-X}}{\text{C-In}} \cdot 100$$

where C-In is the Inulin clearance, and C-X is the clearance of the electrolyte (either sodium or potassium).

D. *Statistical Analysis*

Baseline data was examined for homogeneity between the two test groups (F Test). Homogeneity was found, and in the results section, the pooled baseline data is presented. Similarly, the changes produced by shock were examined and found to be homogeneous between the two test groups. Changes produced by shock and resuscitation in the two test groups were examined by paired "*t*" testing. Differences between the two test groups were examined with standard "*t*" testing. In the results section, means are always presented ± their 95% confidence intervals (95% C.I.). Unless otherwise specified, the expression "a significant difference," refers to a difference where $p < 0.05$.

Results

Hemorrhage and Infusion Volumes: The mean hemorrhage volume was 35.1 ± 3.0 cc./Kg. with no significant difference between groups ($p > 0.05$). The resuscitation volume in the Ringer's group was 147.2 ± 29.0 cc./Kg., and in the albumin group the resuscitation volume was 64.8 ± 9.4 cc./Kg. Thus the infusion volume, hemorrhage volume ratios were 4.2 ± 1.0 in the Ringer's group and 1.9 ± 0.4 in the albumin group. These ratios are significantly different ($p < 0.01$). The mean volume of red cells returned was 15.1 ± 2.6 cc./Kg. with no significant difference between the two groups ($p > 0.05$). These hemorrhage and infusion volumes are comparable to the volumes reported by us in previous studies using similar models.[7,8,15]

Hematocrit: Mean basal hematocrit (Hct.) was 31.7 ± 2.2%. As in our other studies with the same model, shock was characterized by a fall in hematocrit ($\Delta = -9.0 \pm 1.2\%, p < 0.01$).[8] After resuscitation with Ringer's lactate and shed red cells the hematocrits were restored to basal values ($\Delta = -1.2 \pm 1.8, p > 0.05$). However, after resuscitation with 5% albumin and shed red cells, the hematocrit remained significantly depressed ($\Delta = -8.8 \pm 2.9, p < 0.01$). The difference between the two groups was significant ($p < 0.01$).

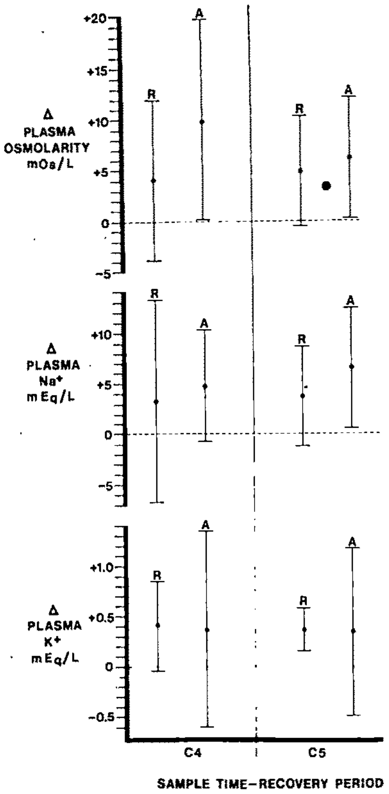

FIG. 3. *Top:* Change in plasma osmolarity after shock and resuscitation. Baseline plasma osmolarity was 291.3 ± 5.9 mOs/L. Shown is the mean change from baseline (±95% C.I.), at collection points C_4 and C_5 during the recovery period in the albumin resuscitated (A) and Ringer's lactate (R) groups. *Middle:* Change in plasma Na^+ after shock and resuscitation. Baseline Na^- concentration was 145.7 ± 3.8 mEq/L. Shown is the mean change from baseline (±95% C.I.) at collection points C_4 and C_5 during the recovery period. *Bottom:* Change in Plasma K^+ after shock and resuscitation. Baseline plasma K^+ concentration was 3.2 ± 0.3 mEq/L. Shown is the mean change from baseline (±95% C.I), at collection points C_4 and C_5 during the recovery period.

Urine Output (Fig. 2)

Mean baseline urine output was 10.2 ± 1.5 cc./Kg./hr. The entire 75-minute shock period was characterized by a significant reduction in urine volume. During the first 15 minutes (induction) there was still moderate urine output (4.3 ± 1.4 cc./Kg./hr.). However, during the remaining 60 minutes there was virtually no urine output (0.3 ± 0.2 cc./Kg./hr.). In the Ringer's lactate resuscitated group, urine output was returned to basal values by the end of the first 30 minutes of resuscitation, followed by a significantly elevated urine output for most of the remaining resuscitation and recovery period. By the end of the study, urine output was indistinguishable from basal value.

In contrast, urine output was not restored to basal values in those animals resuscitated with the 5% albumin until the end of the first 60 minutes (after return of shed red cells). Restoration of urine output, was delayed by 30 minutes in the albumin group as compared to the saline group ($p < 0.05$). During the remainder of the resuscitation and recovery periods, the urine output in the albumin group remained indistinguishable from basal outputs. There was never any diuresis. Despite the large differences in the means, the total post shock urine output in the saline group (70.2 ± 22.0 cc./Kg.) was not significantly different from the total volume in the albumin group (47.3 ± 26.3 cc./Kg.) due to the large variation in volumes. In the saline group, the total urine outputs correlated directly with the resuscitation volumes ($R = +0.94$, $p < 0.01$), but there was no such correlation in the albumin resuscitated group. ($R = +0.08$, $p > 0.05$).

Plasma Osmolarity and Electrolytes (Fig. 3).

Baseline plasma osmolarity was 291.3 ± 5.9 mOsm/L. At the end of the shock period there was a significant rise in osmolarity ($\Delta = +10.8 \pm 5.6$ mOms/L, $p < 0.01$) comparable to that reported in our previous studies.[15] After resuscitation with Ringer's lactate, plasma osmolarity returned to basal values. However, as seen in Figure 3, the plasma osmolarity remained significantly elevated ($p < 0.05$) following resuscitation with the 5% albumin. There was no significant difference between the two groups.

Baseline plasma sodium concentration was 145.7 ± 3.8 mEq/L. Those animals receiving Ringer's lactate had no significant change in their sodium concentrations after shock and resuscitation. Those animals resuscitated with 5% albumin had a significant elevation of their plasma sodium levels at the end of the recovery period. There was no significant difference between the two groups.

Basal plasma potassium concentration was 3.2 ± 0.3 mEq/L. After resuscitation with Ringer's lactate, there was a small but significant elevation in the Plasma K$^+$ level. There was no significant change in plasma K$^+$ in those animals resuscitated with the 5% albumin, and no significant difference between the two groups.

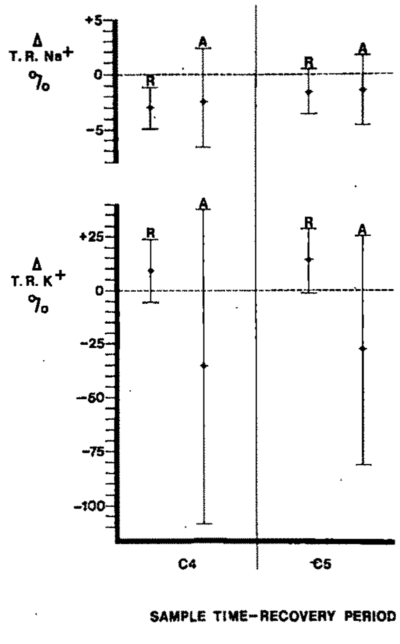

FIG. 4. *Top:* Change in tubular reabsorption (% T.R.) of sodium after shock and resuscitation. Baseline % T.R. of Na$^+$ was 93.2 ± 1.8%. Presented is the mean change from baseline ±95% C.I.), at collection points C_4 and C_5 during recovery in the albumin resuscitated (A) and Ringer's lactate resuscitated (R) groups. *Bottom:* Change in tubular reabsorption of potassium. Baseline % T.R. of K$^+$ was 35.4 ± 12.4%. Presented is the mean change from baseline (±95% C.I.), at collection points C_4 and C_5 during recovery.

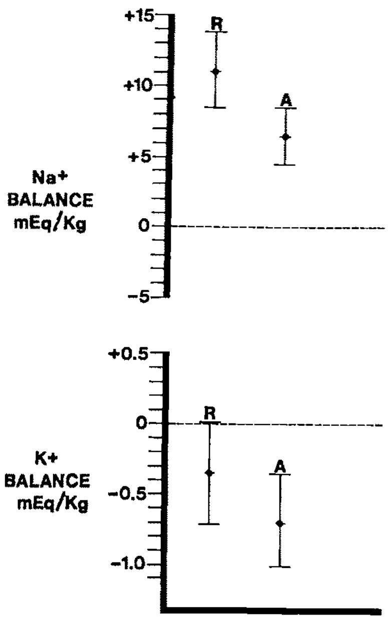

FIG. 5. *Top:* Sodium balance. Shown is the net Na$^+$ balance (±95% C.I.) for the entire resuscitation and recovery periods for the Ringer's lactate resuscitated group (R) and for the albumin resuscitated group (A). *Bottom:* Potassium balance. Shown is the net K$^+$ balance (±95% C.I.) for the entire resuscitation and recovery periods in the two test groups.

Tubular Reabsorption of Sodium and Potassium (Fig. 4)

Basal tubular reabsorption (TR) of sodium was 93.2 ± 1.8%, and basal TR of K$^+$ was 35.4 ± 12.4%. After shock and resuscitation there was no significant change in either the TR of Na$^+$ or K$^+$ in the albumin group. Initially, there was a significant fall in the TR of Na$^+$ in the Ringer's treated group, but by the end of recovery there was no significant change, nor any significant difference from the albumin group. There was no significant change in the K$^+$ TR in the Ringer's treated group, and no difference between the two groups.

Electrolyte Balance (Fig. 5)

Both resuscitative fluids contain about the same concentration of sodium and potassium (Ringer's: Na$^+$ = 131.9 mEq/L, K$^+$ = 4.0 mEq/L; 5% albumin in Ringer's: Na$^+$ = 134.5 mEq/L, K$^+$ = 3.4 mEq/L). During the entire resuscitation and recovery periods, the Ringer's treated group received a total of 20.5 ± 3.8 mEq/Kg. of Na$^+$ and 0.60 ± 0.12 mEq/Kg. of K$^+$. In the albumin resuscitated group, the infusion was 10.0 ± 1.1 mEq/Kg. of Na$^+$ and 0.23 ± 0.03 mEq/Kg. of K$^+$. Thus a significantly greater amount of both Na$^+$ and K$^+$ was given to the Ringer's treated group.

The total urinary outputs of sodium and potassium for the entire resuscitation and recovery periods was 9.4 ± 3.5 mEq/Kg. and 0.95 ± 0.33 mEq/Kg. respectively in the Ringer's treated group, and 3.6 ± 1.7 mEq/Kg. and 0.93 ± 0.33 mEq/Kg. respectively in the albumin resuscitated group. The net sodium and potassium balances are shown in Figure 5. There was a significant positive sodium balance in both groups. The sodium balance in the Ringer's group was significantly higher than the balance in the albumin group ($p < 0.01$). There was no significant shift of potassium in the Ringer's group, but there was a significant negative potassium balance in the albumin group ($p < 0.01$). There was no significant difference between the two groups.

Osmolar Clearance and Free Water Clearance (Fig. 6)

Basal osmolar clearance was 11.0 ± 2.0 cc./Kg./hr. After shock and resuscitation osmolar clearance was initially elevated significantly in the Ringer's treated group, but by the end of recovery, there was no longer a significant difference. In those animals resuscitated with albumin, osmolar clearance was not significantly different from basal values, nor was there any significant difference from the Ringer's resuscitated group.

Basal Free Water Clearance (FWC) was −0.83 ± 1.58 cc./Kg./hr., indicating no significant loss or retention of water at baseline. FWC did not change significantly after resuscitation with Ringer's lactate. However, at the end of the recovery period, FWC was consistantly elevated in those animals treated with 5% albumin ($p < 0.05$). This elevation was also significantly different from the Ringer's treated group ($p < 0.05$).

Renal Blood Flow and Glomerular Filtration Rate (Fig. 7)

Basal Renal Blood Flow (RBF/E) was 43.4 ± 0.3 cc./Kg./min. After shock and resuscitation there was no significant change in the albumin resuscitated group. Although, by the end of the recovery period, there was a significant fall in the RBF/E in the Ringer's treated group, the difference between the two groups was not significant.

Glomerular Filtration Rate (GFR) at baseline was 2.24 ± 0.40 cc./Kg./min. After shock and resuscitation GFR did not change in either test group, nor was there any significant difference between the two groups.

Tubular Extraction of PAH (Fig. 8)

The basal extraction ratio of PAH (E-PAH) was 84.9 ± 4.5%. E-PAH did not change in those animals subjected to shock and resuscitated with Ringer's lactate. However, E-PAH fell significantly ($p < 0.01$) in those animals subjected to shock and resuscitated with the 5% albumin in Ringer's lactate. This fall in E-PAH was significantly different from the results in the Ringer's treated group ($p < 0.01$).

Discussion

We have conducted a series of experiments comparing the effectiveness of physiologic salt solutions and 5% albumin solutions when used for the initial resuscitation from hemorrhagic shock in the sub-human primate.[7,8,9,15,16,17] Earlier studies demonstrated an equal restoration of circulatory, metabolic, and ventilatory indices.[7,17] However, later studies in animals resuscitated with 5% albumin demonstrated an increase in variability of pulmonary water contents,[8] significantly elevated pulmonary water contents[9] and distortion of the alveolarcapillary diffusion membranes.[16] No such changes were seen in animals resuscitated with Ringer's lactate. The clinical significance of the abnormal findings after resuscitation with 5% albumin remains unclear. However, we concluded that resuscitation with physiologic salt solutions, as an adjunct to blood replacement was safe and effective.

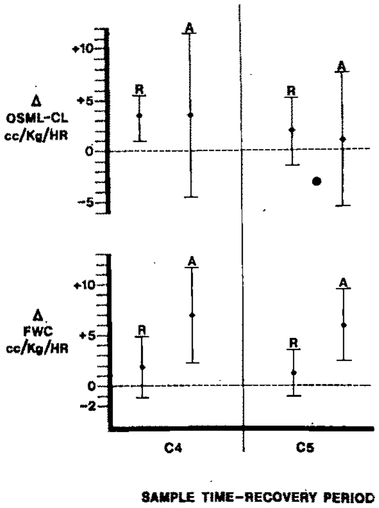

FIG. 6. *Top:* Change in osmolar clearance after shock and resuscitation. Baseline osmolar clearance was 11.0 ± 2.0 cc./Kg./hr. Presented is the mean change from baseline (±95% C.I.) at collection points C_4 and C_5 during recovery in the albumin resuscitated (A) and Ringer's lactate resuscitated (R) groups. *Bottom:* Change in free water clearance (FWC) after shock and resuscitation. Baseline FWC was −0.83 ± 1.58 cc./Kg./hr. Shown is the mean change from baseline (±95% C.I.), at collection points C_4 and C_5 during recovery.

The recent clinical reports of poorer renal function in patients resuscitated with 5% albumin,[2] prompted us to investigate the renal effects of shock and resuscitation with the two test fluids. Shock in this study, as in

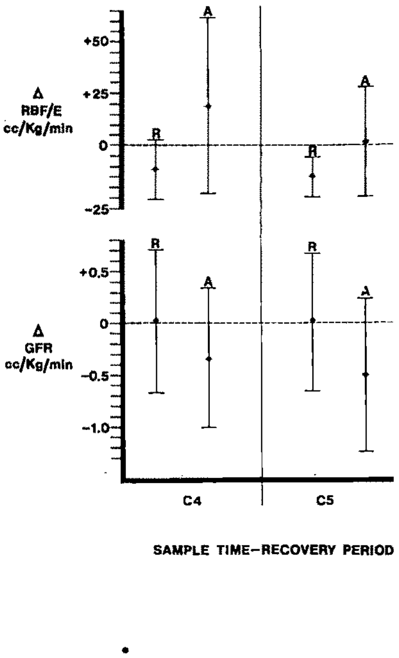

FIG. 7. *Top:* Change in corrected renal blood flow (RBF/E) after shock and resuscitation. Baseline RBF/E was 43.4 ± 0.3 cc./Kg./min. Presented is mean change from baseline (±95% C.I.), at collection points C_4 and C_5 during recovery in the albumin resuscitated (A) and Ringer's lactate resuscitated (R) groups. *Bottom:* Change in glomerular filtration rate (GFR) after shock and resuscitation. Baseline GFR was 2.24 ±0.40 cc./Kg./min. Presented is the mean change from baseline (±95% C.I.), at collection points C_4 and C_5 during recovery.

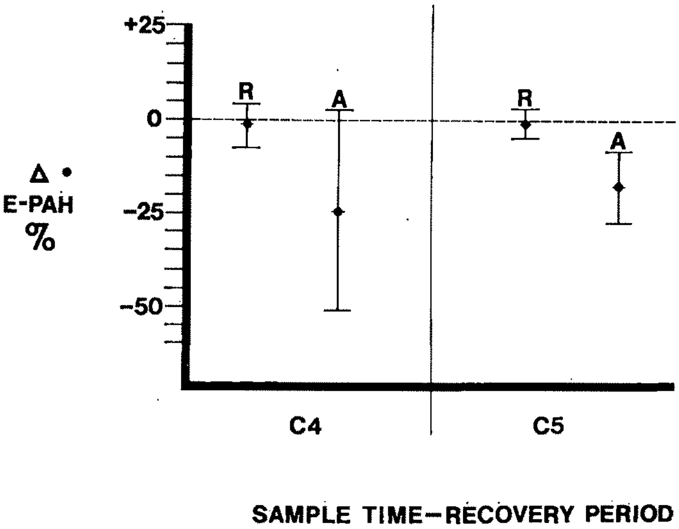

FIG. 8. Change in tubular extraction ratio of PAH (E-PAH) after shock and resuscitation. Baseline E-PAH was 84.9 ± 4.5%. Presented is the mean change from baseline (±95% C.I.) at collection points C_4 and C_5 during recovery in the albumin resuscitated (A) and Ringer's lactate resuscitated (R) groups.

our previous studies,[8,15] was characterized by a rising plasma osmolarity, hemodilution, and virtual anuria. It is clear that the kidneys are thus maximally stressed.

The more rapid return of the urine output in those animals resuscitated with Ringer's lactate is striking. Since renal tubular function in this group is returned to normal and since the urine outputs are correlated with the infusion volume, it is obvious that this rapid return of urine outputs, and the subsequent diuresis, is not high-output renal failure, but rather a normal response to the large fluid volumes infused. What is distressing is that in the albumin resuscitated group there is no return to basal urine outputs until after the red cells have been returned, suggesting that the albumin is less effective in restoring renal function.

The sustained significant depression of the hematocrit in the albumin treated animals is indicative of an expanded intravascular volume, since all the shed red calls were returned. This expanded intravascular volume has been a consistent finding in our previous studies.[7,8] However, the rise in plasma osmolarity and sodium in the albumin group suggests that this expanded intravascular volume is hypertonic. Such a hypertonic plasma should be a powerful stimulus for water conservation in a normal functioning kidney. The lack of correlation between infusion volumes and urine volume, and the inappropriate increased free water clearance in the albumin group suggests tubular dysfunction. The normal plasma osmolarity and plasma sodium concentration, and normal FWC in the Ringer's group is further evidence that the diuresis is compensatory to establish normal water and electrolyte balance.

Since the total sodium infusion was higher in the Ringer's group, and since the positive sodium balance was greater in the Ringer's group, it is surprising that the albumin group, with its expanded intravascular volume, has a significantly elevated plasma sodium while there is no such elevation in the Ringer's group. Since there is no increase in tubular reabsorption of Na$^+$ in the albumin group, the only explanation of the rise in the plasma Na$^+$ is the inappropriate free water clearance.

It is not surprising that there is a significant positive Na$^+$ balance in both groups. It has been shown that shock, and the immediate post-shock period is characterized by an increased affinity of the interstitial collagen for sodium, with a net increase in interstitial sodium.[6,10] The excess sodium in the Ringer's group appears to be well handled, with an initial drop in the tubular reabsorption of Na$^+$ and a corresponding rise in osmolar clearance. The lack of a significant change in either Na$^+$ reabsorption or osmolar clearance in the albumin group probably reflects the smaller sodium load and the smaller sodium excess.

The meaning of changes in K$^+$ reabsorption is not clear, except that with normal tubular function any change in Na$^+$ reabsorption is usually compensated for by an opposite change in K$^+$ reabsorption.[1,5] In the Ringer's treated group, the mean fall in tubular reabsorption is associated with a mean rise in K$^+$ reabsorption. Studies in dogs have shown that kidneys subjected to hypoxia exhibit a fall in absorption of both Na$^+$ and K$^+$.[13] In the albumin resuscitated group the mean fall in tubular reabsorption of Na$^+$ is associated with a mean fall in K$^+$ reabsorption. This suggests tubular dysfunction in the albumin resuscitated group, and no such tubular dysfunction in the Ringer's lactated treated group.

The lack of any significant differences between the two groups with respect to RBF/E and GFR is not surprising. In previous studies we have commented on the large variability and unreliability of RBF/E and GFR.[15] Although there was a significant fall in RBF/E in the Ringer's treated group, the mean value at the end of the day (27.8 ± 9.6 cc./Kg./min.) is still within normal limits for baboons,[15] and still adequate for renal perfusion. The adequacy of the perfusion is clearly seen since there is no evidence of any tubular dysfunction in the Ringer's treated group. However, the unchanged RBF/E in the albumin group does not prevent the appearance of tubular dysfunction.

The extraction ratio is a better, more accurate estimate of renal tubular efficiency.[1,3,5,11,14,15,18] The normal E-PAH after shock and resuscitation with Ringer's lactate is clear evidence of normal tubular efficiency in that group. Studies in patients and animals have shown that E-PAH is depressed only when there is either tubular damage or when there is significant pretubular shunting of blood.[3,5,11,14,18] Other studies in humans have shown that the infusion of albumin caused a rise in renal blood flow and a fall in E-PAH.[4] This was explained as a function of pretubular shunting. Our previous studies have demonstrated a fall in E-PAH in animals resuscitated with 5% albumin, no change in RBF/E, and no evidence of increase pretubular shunting, based on arterial-renal vein O_2 gradients.[15] In this study the lack of any change in GFR, and the increase in FWC in the albumin group is inconsistent with any increase in A-V shunting. Thus, it seems inescapable that the fall in E-PAH after shock and resuscitation with 5% albumin is indicative of severe tubular dysfunction.

We conclude that resuscitation from hemorrhagic shock with a balanced salt solution in conjunction with red cell replacement effectively restores normal renal tubular function. In contrast, there is evidence that resuscitation with 5% albumin and red cells is not as effective in restoring renal tubular function.

Summary

A comparative study was carried out in 13 awake baboons with chronically implanted renal vein catheters. Shock was induced by a 15-minute hemorrhage to reduce mean arterial pressure to 50 mm. Hg. This pressure was maintained for 60 minutes. Resuscitation was carried out over a 90-minute period, using either Ringer's lactate followed by shed red cells, or 5% albumin followed by shed red cells. Resuscitation was sufficient to restore baseline vascular pressures.

In those animals resuscitated with Ringer's lactate, there was a return of urine output to basal values within 30 minutes, normal electrolyte and water balance, and normal renal tubular function as judged by the extraction ratio of PAH. While renal blood flow was reduced, perfusion was still adequate, and glomerular filtration was unchanged.

In contrast those animals resuscitated with 5% albumin demonstrated a significantly slower return to basal urine outputs, an increased intravascular volume, with an increase plasma osmolarity and sodium concentration. Renal tubular absorption of Na^+ and K^+ were both depressed, suggesting tubular inefficiency in handling electrolytes. There was an inappropriate increase in free water clearance, despite the hyperosmolar, hypernatremic plasma. Renal blood flow and GFR were unchanged. Despite the unchanged renal blood flow, there was a significant reduction in E-PAH that cannot be explained on the basis of shunting.

It is concluded that resuscitation from hemorrhagic shock with a balanced salt solution in conjunction with red cell replacement is more effective in restoring normal renal tubular function than resuscitation with a colloid solution.

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Wound Complications in Recipients of Renal Transplants

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IMPAIRED HEALING of wounds in recipients of renal transplants can be caused by several factors. The patients are often edematous, protein-depleted and anemic from uremia. In addition, decreased wound healing and increased susceptibility to infection is caused by immunosuppressive therapy.[9,16] Wound infections have been reported to occur in 10 per cent to 39 per cent of transplant recipients[11,15] and complications of wound healing often lead to other serious or fatal complications. An understanding of the etiologic factors of these complications and their management may lessen their occurrence and significance.

Material and Methods

A study was made of the operations performed on 178 renal transplant recipients at the University of California, San Francisco, between January 1968 and February 1971. This period was chosen because the problems of overimmunosuppression in an earlier period had become recognized and because a prospective study of local antibiotic prophylaxis had just begun by one of the authors (F.O.B.) In one half of these patients antibiotic solutions were placed in the wound at the time of transplantation. Local antibiotics consisted of 50,000 units of bacitracin and 1 Gm. neomycin in 200 ml. of saline for irrigation of all layers of the abdominal wall; then the same antibiotics were administered in 50 ml. of saline to cover the subcutaneous layer after closure of the muscle and deep fascia. The perinephric area was not irrigated with antibiotics except in certain contaminated wounds.

The operative technics otherwise followed the standard procedures: renal transplants in adults were placed in pelvic retroperitoneal areas through lower abdominal oblique incisions, or in children through midline laparotomy incisions. Electrocoagulation was used for hemostasis in the subcutaneous and muscle layers, and silk ligatures were used on all other vessels. Drains were not routinely inserted in primary transplant wounds. Wounds were closed with a running chromic catgut suture for the muscle and deep fascial layer and interrupted silk for the fascia of the external oblique. Scarpa's fascia was approximated with a few interrupted 000 plain catgut sutures and the skin was closed with interrupted nylon sutures. Skin sutures were removed on the 14th postoperative day. Similar technics were used in other major surgical wounds in these patients. Standard immunosuppression consisting of azathioprine and prednisone was used, and Actinomycin D and graft irradiation were given for threatened rejection.

Results

A total of 331 major operations were performed on 178 patients on immunosuppressive therapy during the 3-year period. Thirty septic complications developed in these wounds, including full-thickness wound infections as well as perinephric abscess and infected hematomas, for an incidence of 9 per cent (Table 1).

Uncomplicated Transplant Wounds. Of the 210 renal transplants performed on these 178 patients, 175 of the transplant wounds had no complications other than three infections, an incidence of 1.7 per cent (Table 2). One of these was a perinephric abscess presenting 3 months after transplantation. These three infections developed in a series of 79 wounds in which local antibiotics were

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not used. In one case infection contributed to the patient's death. No wound infections occurred in 96 transplant operations in which local antibiotics were used.

Reopened Transplant Wounds. Clean transplant wounds were reopened for a variety of reasons such as for hematomas or rejected grafts (Table 3). Most of these wounds were reopened within the first few weeks after transplantation, but also included are transplant nephrectomy wounds which in a few cases were reopened several months after transplantation. Of a total of 119 such wounds, 22 developed septic complications, an incidence of 18.5 per cent.

Wounds with large hematomas and those in which a transplant nephrectomy was performed were particularly susceptible to septic complications. The hematomas will be discussed later in more detail. Of the 58 wounds incurred during transplant nephrectomy, 10 became infected (17%). Six of these were deep in the wound and three were associated with hematomas. All infected transplant nephrectomy wounds grew common gram-negative microorganisms. In one patient infection after transplant nephrectomy was a major contributing factor to death.

In 15 major operations the urinary tract was intentionally opened. None of these wounds became grossly infected despite the frequently infected urine and occasional septicemia following the operative procedure. Systemic antibiotics were often given and topical antibiotics were used in seven of these wounds. Seven other urologic procedures were performed on four patients for uretero-cutaneous fistulas. Two of these fistulas followed wound infections and one followed a perinephric abscess secondary to a colon perforation. Since these procedures resulted from septic complications, they are not included in the results. The other fistula occurred during drainage of a lymphocele. This wound became infected and is included in the tabulation of the results.

Laparotomy Wounds. Ninety-six laparotomies were performed for recipient bilateral nephrectomy and splenectomy before renal transplantation, while the patients were not on immunosuppressive therapy. Two superficial wound infections occurred in this group (2%). Twenty-one laparotomies were performed after transplantation in which there was no contamination of the wound. No wound complications developed in these 21 operations. Sixteen operations were performed in eight other immunosuppressed recipients in whom the laparotomy wound became grossly contaminated, as, for example, from resection of gangrenous bowel or drainage of intra-abdominal abscesses. Five of these wounds became infected (31%). Three wounds were left open for a delayed closure, and six patients died soon after operation. Thus, the eventual incidence of wound infection in these patients might have been higher.

TABLE 1. *Septic Wound Complications in Immunosuppressed Patients*

	Total Number	Number Infected	Per Cent
Primary transplant wounds	175	3	1.7
Reopened transplant wounds	119	22	18.5
Uncontaminated laparotomies	21	0	0.0
Contaminated laparotomies	16	5	31.2
	—	—	
Combined totals	331	30	9.0*

* = percentage of wounds infected in all procedures.

Wound Hematomas. Twenty-eight hematomas occurred in the deep retroperitoneal wound in 23 patients (13%), or 9.5 per cent of 294 operations. Twelve of these patients received kidneys from cadaver donors and 11 from living donors. Twenty-three hematomas developed within the first 2 weeks after transplantation and five after transplant nephrectomy. Fourteen patients had acute tubular necrosis, 11 of whom received cadaver kidneys. Hemodialysis performed in the post-transplant period because of acute tubular necrosis or a severe rejection episode was the probable cause in 17 of 28 hematomas (60%). Other causes were a diffuse bleeding diathesis in two patients and technical problems in nine cases. Technical problems included vessel anastomotic leaks or inadequate deep wound hemostasis, and were occasionally associated with a bleeding diathesis.

Twelve of the hematomas became infected (43%), nine of these were in transplant wounds and three in transplant nephrectomy wounds. Penrose drains were used in 15 of the hematomas (54%) and were associated with 75 per cent of the infected wound hematomas (Table 4). Seven of the hematomas were treated by evacuation of clot, thorough irrigation of the entire wound with saline and topical antibiotics and primary deep wound closure, and none became infected. Two of the hematomas treated in this manner were infected at the time of wound exploration and the patient had delayed primary closure of the subcutaneous wound without subsequent sepsis. One of the hematomas was suppurative at the time of wound exploration and the transplanted kidney was abscessed; the entire wound was left open. One small, liquified hematoma was treated by needle and syringe aspiration and did not become infected.

TABLE 2. *Septic Complications in Transplant Wounds*

Type of Wound	Total Number	Number Infected	Per Cent
A. Primary (single procedure)	175	3	1.7
1. No local antibiotics given	79	3	3.8
2. Local antibiotics given	96	0	0.0
B. Reopened	119	22	18.5
1. No local antibiotics given	70	20	28.6
2. Local antibiotics given	49	2	4.0
C. Combined totals	294	25	8.5

TABLE 3. *Reopened Transplant Wounds*

	Total Number	Number Infected	Per cent
Evacuation or drainage of hematomas following transplantation	22	9	41
Transplant nephrectomy (Including those with hematomas)	46	8	17
Transplant nephrectomy and retransplant	12	2	17
Urologic procedures (clean contaminated)	15	0	0
Lymphoceles	9	1	12.5
Open renal biopsies	8	1	
Miscellaneous reexplorations	7	1	
Totals	119	22	18.5

All 12 infections cultured gram-negative microorganisms and in ten of the 12, the organisms were the same as those found in earlier or concomitant urinary cultures. One wound infection cultured staphylococcus and pseudomonas.

The infections resulting from these hematomas caused a uretero-cutaneous fistula in one patient, resulted in the loss of one kidney in another patient, and were major contributing factors in the deaths of three patients (9% of the 34 deaths in the entire series). The hypotension and decreased renal perfusion occasionally resulting from acute hemorrhage in the wound caused tubular necrosis in four patients.

Lymphoceles. This complication occurred in 2.4 per cent of the retroperitoneal renal transplant wounds. It will be reported elsewhere[14], and will only be summarized here. Nine lymphoceles developed in six patients, and were diagnosed between 18 days and 6 months after transplantation by intravenous pyelograms. All caused some degree of renal function impairment which improved following drainage. Penrose drains inserted through a small incision were sufficient therapy for most lymphoceles, but two patients had recurrences. In one patient a third recurrence was treated by intraperitoneal marsupialization.

TABLE 4. *Management of Wound Hematomas*

Method	Total Number	Number Infected
A. Penrose drains	15	9
B. Evacuation, local antibiotics and primary closure	7	0
C. Needle aspiration	1	0
D. (Septic at exploration)		
1. Wound left open	1	1
2. Closed (as in B)	2	0

Discussion

Both clinical observations and experimental studies indicate that wounds in uremic and heavily immunosuppressed patients are more susceptible to infection and to delayed wound healing.[6,9,11,15,16] However, our results with wounds in 178 renal transplant recipients indicate that these complications can be kept low if the problems of wound hematomas and of transplant nephrectomy wounds are prevented or properly managed. A septic wound complication rate of 2.8 per cent occurred in transplant wounds which did not develop hematomas or involve a rejected kidney.

Several measures can be taken which we believe will result in a low infection rate. One is to avoid using Penrose drains whenever possible. The presence of this foreign body and the possibility of its acting as a conduit for bacterial contamination of the deeper wound from skin bacteria, as has been clearly demonstrated in animal experimental wounds,[4] seems to contraindicate its use. Their prophylactic use for potential urinary leaks is not warranted since these are infrequent when ureteroneocystostomy is used for re-establishing the urinary tract.[2] Penrose drains are unlikely to drain a developing deep wound hematoma effectively and do not prevent pelvic lymphoceles.[13]

Another measure which seems to be of value is the use of local antibiotic solutions. One of the major defects in the immunosuppressed wound appears to be its poor ability to phagocytize and kill bacteria due to neutrophil dysfunction.[1] Thus, the small amount of bacterial contamination which is present in most operative wounds[19] may be more than the immunosuppressed wound can effectively handle. Topical antibiotics would then add the extra margin of safety by helping to sterilize the wound. The choice of antibiotics and the dose follow the general rule for the selection of any antimicrobial agent: that it be relatively nontoxic, in sufficient concentration in the area of contamination, and capable of killing or inactivating the contaminating organisms.

The results of the use of bacitracin and neomycin applied locally to wounds in transplant recipients is encouraging. There were only two septic wound complications in 145 procedures in the patients who were given local antibiotics, and in the group not given local antibiotics, there were 149 wounds and 23 septic wound complications. The difference between these groups is statistically significant ($p < 0.001$). However, we cannot conclude that this difference is due to the antibiotics alone, since different surgeons performed the procedures with differences in technic other than the use of antibiotics.

Starzl used the same combination of antibiotics with satisfactory results,[15] and good results from the use of these antibiotics in contaminated wounds were reported by Glotzer *et al.*[5] Also important is that these antibiotics caused no harm. Side effects from drugs were no different in these patients than in the control group.

Other means to prevent wound infection are those common to all surgical wounds: that dead space be avoided, that tissues be handled gently, and that hemostasis be present. The latter is especially important in transplant wounds.

Deep wound hematomas are serious complications in transplant wounds, as indicated by the high incidence of infection of 43 per cent. Certainly every effort must be made to prevent their formation. Most uremic patients have a bleeding tendency due primarily to reduced platelet adhesiveness.[8] Dialysis, platelet transfusions, and fresh blood transfusions are measures which may be used to control this problem. A few patients will be on long-term anticoagulation because of arteriovenous shunt clotting problems, which must be partially corrected before surgery. We have found that the organ preservation methods used at this center permit time for preoperative dialysis and for partial reversal of anticoagulation in the proposed recipients.

However, most hematomas are caused by post-transplant dialysis, in spite of regional heparinization during hemodialysis. Acute tubular necrosis in cadaveric kidney transplants is the most frequent reason for this dialysis. Although the incidence of tubular necrosis could be lowered by careful selection and preparation of cadaver donors,[3] the scarcity of otherwise suitable cadaver donors does not permit such selection. Therefore, the primary mode of prevention must be carefully conducted regional heparinization during hemodialysis, with adequate follow-up in the immediate postdialysis period. Since a transient anticoagulant period may develop several hours after termination of hemodialysis, this must be watched for and appropriately treated.[7] Some of the hematomas are due to faulty surgical technic, and could be prevented.

We believe that the method of choice in management of deep wound hematomas is careful evacuation of the hematoma in the operating room, with saline and antibiotic irrigation, and primary closure without drains. One patient had two such procedures without infection or other complications. Simply introducing a Penrose drain into a large deep wound hematoma, with the expectation that it will adequately drain, often results in an infection in that hematoma.

The transplant-nephrectomy wound is also a major cause of wound sepsis in renal transplant patients. Moore and Hume reported an infection rate of 56 per cent in these wounds.[12] The high infection rate is caused by: 1) the need for postoperative hemodialysis with an increased incidence of deep wound hematomas; 2) the presence of an often necrotic and occasionally septic rejected renal graft; 3) increased immunosuppression in an attempt to reverse the rejection episode; 4) difficulty in obliterating the space left after nephrectomy; and 5) difficulty in completely removing adherent allografted tissues.

To lessen the chance of gross infection of the rejected kidney, we now perform nephrectomy as soon as the renal scan indicates no significant renal blood flow. Only three out of the 11 infected transplant-nephrectomy wounds occurred in the last 2 years, since earlier nephrectomy has been performed. Another useful measure is to use local antibiotics in these wounds since two of the transplant-nephrectomy wounds which were infected at the time of operation did not subsequently become infected when so treated.

Systemic antibiotics were not routinely used, but they appeared useful when a specific microorganism was known to be present. For example, in several patients with chronic staphylococcal infection of their arteriovenous shunts, an antistaphylococcal antibiotic given before and after operation may have prevented wound infection. The situation was similar in urinary tract infections. Broad-spectrum prophylactic antibiotics are not advocated as they may be dangerous in postoperative immunosuppressed patients because they encourage the growth of resistant bacteria and fungi, and may often be nephrotoxic.[17,18]

The diagnosis of deep wound infection or perinephric abscess is sometimes difficult in the patient on corticosteroids. Once detected, however, the wound must be widely opened and frequently irrigated in an attempt to prevent erosion into the exposed vessels or transplant ureter. Wound contraction and epithelization in the patient on steroids are delayed, but topical vitamin A therapy after the infection has been controlled may aid in epithelization.[10] Wound contraction will progress slowly, and considerable patience and continued local care of the wound are required.

Summary

Thirty septic wound complications occurred in 331 major operations performed in 178 renal transplant recipients (9% incidence). Wound hematomas and transplant nephrectomy wounds were associated with most of these complications. Primary transplant wounds, when otherwise uncomplicated, had an infection rate of 1.7%.

Measures to reduce the incidence of septic wound complications in these immunosuppressed patients include the avoidance of drains, carefully managed regional anticoagulation when hemodialysis is required, and the use of local antibiotics. Wound hematomas are best managed by evacuation of the hematoma and primary wound closure without drains. Transplant nephrec-

tomies should be performed before the rejected graft becomes septic.

Lymphoceles occurred in 2.4% of transplant wounds. They are best treated by insertion of Penrose drains, and can be prevented by ligation of divided lymphatics.

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Blood Flow Measurements during Repair of a Right Coronary Artery Superior Vena Cava Fistula

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ANOMALIES of the coronary arteries constitute an uncommon but sometime correctable form of congenital heart disease. To date, 117 cases of congenital coronary arteriovenous fistula have been reported in the world literature.[10]

This paper reports a case of an aneurysmal fistulous connection between the right coronary artery system and the superior vena cava in which operative flow measurements were obtained before and after surgical correction.

Case Report

L. H., #179260. A 34-year-old woman was in excellent health except for the usual childhood illnesses. At age 22 on a routine examination she was noted to have a heart murmur. She had two pregnancies with no difficulties. In November, 1968, she noted the onset of palpitations. Since that time, particularly in May and June, 1970, she had intermittent palpitations associated with a thoracic tightness described as a band around her chest. The episodes lasted from seconds to a minute, occurring 10–15 times per day. On physical examination, recumbent blood pressure in each arm and leg was 110/70. Carotid pulses demonstrated a slightly exaggerated upstroke time. Neck veins were flat. Heart tones were normal; there was an S_1 and S_2 with no S_3 or S_4 gallop. There was normal splitting. The left border of cardiac dullness was 9 cm. from the midsternal line. There was a high frequency murmur heard best in the aortic area. The murmur began early in systole, continued through the second heart sound and diastole, and was crescendo-decrescendo at about the second heart sound. Routine laboratory tests and electrocardiograms were normal. Complete right and left heart catheterization with ventriculography and selective coronary arteriography was performed. Coronary angiography revealed a fistulous connection between a dilated main right coronary artery and the superior vena cava. The hemodynamic data and oxygen gradient are listed in Table 1.

Elective cardiac surgery was performed in January 1971 and the findings were as follows: The left coronary artery appeared normal. The proximal right coronary artery was approximately 9 mm. in diameter and was dilated from its origin to the junction of the ramus osti cavae superioris (sino-atrial node artery). The distal right coronary artery was normal in size and location. The sinoatrial branch of the right coronary artery was also markedly dilated and tortuous. It contained a palpable systolic and diastolic thrill. It coursed tortuously over the right atrium and terminated in the medial aspect of the proximal superior vena cava (Fig. 1A).

An 8.5 mm. electromagnetic flow probe was placed around the dilated main right coronary artery proximal to its S.A. nodal branch (Fig. 1B). Flow zero was obtained by temporary occlusion of the vessel distal to the probe. Flow measurements* were taken with the S.A. node branch open (Fig. 2A) and occluded (Fig. 2B). Blood flow through the fistula was approximately 26% of the total right coronary artery flow.

The dilated S.A. node artery was temporarily occluded for 10 minutes. No cardiac arrhythmias occurred during this period. The S.A. node artery was then transected at its junction with the right coronary artery and the cut ends oversewn proximally and distally (Fig. 1C). The thrill felt over the right coronary artery disappeared following repair. The pericardium was loosely closed, drainage tubes inserted, and the chest closed. The patient made an uneventful recovery and was discharged.

Discussion

Congenital anomalies of the coronary arteries are rare but frequently correctable.[9,15] These anomalies occur in various forms, including fistulous communication, absence, unusual origin, abnormal distribution, aneurysmal formation, and stenosis or occlusion.[7] An excellent review and classification of congenital coronary arteriovenous fistulas has been presented by Horiuchi.[10]

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* Sinai Hospital of Detroit, Detroit, Michigan.

* Biotronex Laboratory 620 Electromagnetic Flow Meter.

TABLE 1

Site	Pressure	O_2SAT	Vol % O_2
HSVC	(6)	77	13.6
HRA	(6)	73	12.8
MRA		74	13.1
LRA		72	12.7
•SVC	(6)	71	12.5
RMPC	(8)	95	17.5
LSPC	(9)		
MPA	20/9 (13)	74	13.1
RV Inflow	20/0–5	71	12.5
RV Outflow		70	12.3
LV	115/07–10		
BA	110/60	94	16.5

Pulmonary blood flow —4.8 l/min
Systemic blood flow —3.5 l/min
Pulmonary arteriolar resistance index—128 dynes/sec/cm^{-5}
Left to right shunt —1.3 l/min
Pulmonary/Systemic flow ratio —1.4:1

HSVC—high superior vena cava
HRA—high right atrium
MRA—mid right atrium
LRA—low right atrium
SVC—superior vena cava
RMPC—right med pulmonary capillary wedge
LSPC—left superior pulmonary capillary wedge
MPA—main pulmonary artery
RV Inflow—right ventricular inflow
RV Outflow—right ventricular outflow
LV—left ventricle
BA—brachial artery

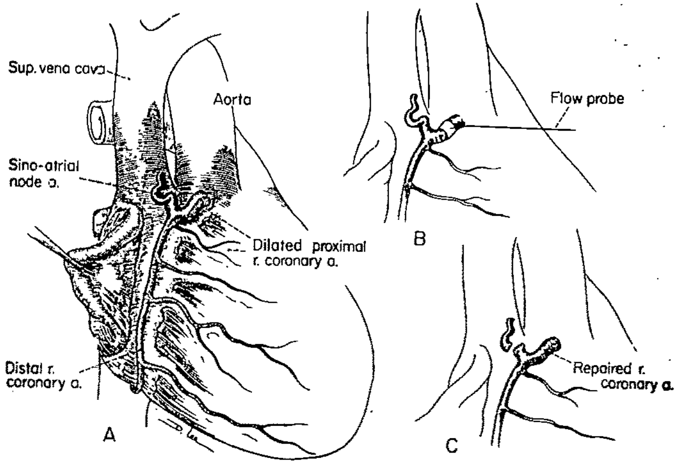

FIG. 1. A, B, C.

The most common type of coronary artery anomaly is one in which a fistulous communication exists between the right coronary artery and a low pressure cardiac chamber. Flow of blood from the high pressure artery into the low pressure chamber occurs in both systole and diastole, and may be associated with a continuous murmur and symptomatology of varying severity.[2,4,12] Hazards of coronary artery fistula include subacute bacterial endocarditis,[8,14,17] coronary artery steal,[16] aneurysm formation with possible rupture,[1] and those problems associated with any left to right shunt. Because of these considerations, there is general agreement that such fistulas be repaired.[1,3,5–7,9–11,13–17]

Simple ligation of the coronary artery proximal and distal to the fistula is generally the operative procedure of choice.[5,7,9,10,13,15] Prior to definitive repair, there should be a preliminary 10 to 15-minute period of occlusion of the fistulous segment with simultaneous electrocardiographic monitoring to ascertain that myocardial ischemia or conduction defects do not occur. If detrimental EKG changes are demonstrated during the preliminary period of occlusion, then repair by simple ligation should be abandoned. Alternate methods of repair include tangential arteriorrhaphy,[9] intracardiac repair, and fistulous ligation with aorto-coronary artery bypass.

In the patient described above, 26% of the total right coronary artery blood flow was "stolen" by the fistula. Transection and oversewing of the cut ends of the fistula was sufficient to reduce the volume of right coronary artery blood flow to normal values. Multiple fistulous communications are often present and difficult to demonstrate radiographically or at operation. Operative blood flow measurements proximal and distal to the area of fistulization can accurately determine the volume of blood diverted through the fistula. Definitive surgical repair is accomplished when the volume of blood flow through the proximal coronary artery is equal to the blood flow through the distal artery. Thus the use of operative blood flow monitoring technics allowed the authors to determine accurately the extent of coronary artery fistulization. In the above patient, ligation of the obvious, large fistula equalized the volume of blood flow proximal and distal to the fistula and eliminated the necessity of further surgical dissection in search for smaller fistulas.

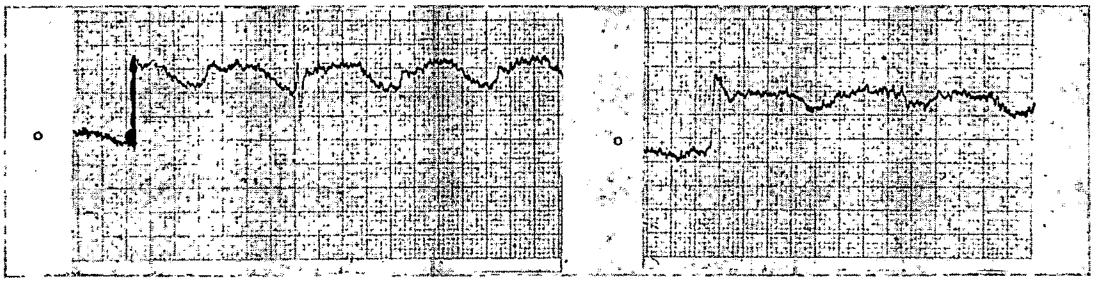

FIG. 2. A (left) Represents main right coronary artery blood flow prior to repair of fistula. B (right) Following repair of fistula. Approximately 26% of the main right coronary artery blood flow was "stolen" by the fistula.

Summary

A case of a right coronary artery superior vena cava fistula which was surgically repaired is presented. Intraoperative blood flow measurements allowed accurate determinations of the extent of fistulization and eliminated unnecessary surgical dissection.

Complications of uncorrected coronary arteriovenous fistulas and various technics of operative repair are briefly discussed.

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Blunt Trauma Rupture of the Heart

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BRIGHT AND BECK in 1934,[3] reported a series of 168 post-mortem cases of cardiac injury. One hundred and fifty-two patients in this series had rupture of one of the cardiac chambers. They pointed out that 30 of this group with chamber rupture lived longer than 1 hour after injury and predicted that with increasing development of cardiac survery, these patients could be salvaged. DesForges,[4] in 1955, reported the first surgical salvage of a blunt trauma right atrial rupture. Since that report,[1,2,5,7,8] six additional cases have been reported, documenting the possibility of salvaging those patients with ruptured cardiac chambers (excluding traumatic septal defects). We are adding a report of three cases to the seven previously reported.

Case Reports

Case 1. R. H. A 23-year-old man was brought to the emergency room after injury in an automobile accident on 11-23-70. He was disoriented, hysterical and could not perceive oral commands. There was no obtainable blood pressure, pulse was rapid but regular. The neck veins were distended with the patient elevated 30°. There was cyanosis over the thorax and upper extremities, neck and face. There was a red band-like abrasion across the upper chest. The abdomen was soft with normal bowel sounds. A chest x-ray demonstrated a normal cardiac and aortic silhouette (Fig. 1). There was no pneumothorax, rib fracture, or hemothorax. The admission hematocrit was 38.5%. A central venous line was inserted into the internal jugular vein, revealing a pressure of 25 cm. H_2O. With this finding and the presence of shock, a pericardial tap returned dark red blood which elevated the blood pressure for a short period of time. Blood pressure again deteriorated, however, and he underwent operation 1 hour after admission. The pericardium was opened through a sternal splitting incision. There was a large amount of blood in the pericardial sac with heavy bleeding from a tear in the right atrium at its juncture with the inferior vena cava. This area was occluded and the patient was infused with blood through a Levine tube placed in the right atrial appendage which brought the blood pressure up to 100 mm. Hg. He received 8 pints of blood. The atrial tear was repaired and the chest was closed. The hematocrit after 8 units of blood was 37.9%. Postoperative course was stable and he left the hospital 7 days after admission. EKG pattern on the day of injury showed non-specific ST-T changes which were gradually resolved by the time of discharge 7 days later. The cardiac muscle enzymes were transiently elevated in the postoperative period. He was seen in follow-up clinic 1 month later with no problems.

Case 2. T. A. A 26-year-old man was riding his motorcycle on the freeway, and struck the rear of a parked car. He was brought to the emergency room on 5-16-71, with initial vital signs demonstrating a heart rate of 124, respirations of 44, and with no obtainable blood pressure. He had a compound fracture of the left lower leg, and several small scalp lacerations. He was slightly disoriented and moderately cyanotic. The chest was clear on auscultation. Cardiac examination revealed distant heart sounds, and no murmurs. Initial examination revealed a soft abdomen with normal bowel sounds. A CVP line which was inserted in the cephalic vein indicated 24 cm. of water. The chest x-ray later showed this still to be in the neck (Fig. 2). There was no cardiac enlargement on x-ray. Blood pressure rose to 60 mm. Hg with 2 liters of Ringer's lactate. Four hours after admission, blood pressure was still in the 60–80 mm. Hg range. By the time he had received 4 liters of Ringer's lactate, his bowel sounds were absent and the abdomen was somewhat distended. An abdominal tap returned bloody fluid. After immediate transfer to the operating room, he was transfused with several units of blood before he was anesthetized, increasing the pressure to 90 mm. Hg. During abdominal prep he was cyanotic over the chest, neck and face. The abdomen was opened with a midline incision revealing a lacerated liver on the undersurface at the insertion of the falciform ligament which was bleeding freely, but there was not enough blood in the abdomen to account for the degree of shock. At this point 4 units of blood had been transfused and blood pressure completely disappeared. An internal jugular vein catheter was then inserted percutaneously and fed into the right atrium with a pressure reading of 54 cm. of water. With this finding the diagnosis of cardiac tamponade was confirmed. The pericardium was opened

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by incising the diaphragm in the midline and opening into the pericardium through the abdomen. A great deal of blood was released from the pericardium, and the blood pressure immediately returned to 100 mm. Hg. Due to the fact that the blood continued to flow heavily from the open pericardium, the sternum was split. Upon opening the pericardium, a laceration of the apex of the right atrial appendage was bleeding freely. It was simply clamped and the laceration was oversewn. Following this procedure there was no further bleeding or other evidence of cardiac injury. A mattress suture was placed over Teflon bolsters to control the hemorrhage from the liver laceration. The rest of the intraabdominal examination was negative. Open reduction of the left tibia and fibula fracture was carried out with internal fixation and fasciotomies. The early postoperative course was entirely benign and he subsequently made an uneventful recovery except for slow healing of the left leg.

Case 3. J. S. A 40-year-old man was involved in an automobile accident on 6-11-71, suffering chest and facial injuries. He was admitted to an outlying hospital with a deep laceration of the right side of the face. During evaluation he went into shock. IV's were started and the blood pressure responded. Chest x-rays at that time showed a left pleural effusion and suggestion of a wide mediastinum (Fig. 3). He was immediately transferred to Santa Clara Valley Medical Center with a physician in attendance. The diagnosis was aortic rupture. Blood pressure on admission was 70/50 mm. Hg. A central venous catheter indicated 14 cm. of water. Repeat chest film demonstrated more pleural effusion. Following this he went into shock with blood pressure falling below 60 mm. Hg, and at that time the venous pressure increased to 20 cm. of water. Pericardial tap returned 30 cc. of bloody fluid and a left chest tube was inserted returning 1,300 cc. of blood. Fifty-five minutes after admission he underwent exploratory surgery through a median sternotomy. At the same time preparations were made for cardiopulmonary bypass. There was a 2 cm. tear in the outflow tract of the right ventricle and the heart was protruding into the left chest through a pericardial tear. The pericardial tear was 10 cm. long, parallel to and posterior to the phrenic nerve. The cardiac laceration was repaired with mattress sutures. It was necessary to repair the long pericardial tear to prevent further incarceration of the heart in the left chest. During the elevation of the heart to repair the tear, he developed arrhythmia. It was deemed necessary to place him on cardiopulmonary bypass after which the pericardial laceration was repaired. A double fracture of the upper sternum was wired. The sternotomy incision was extended into the upper abdomen for exploration. There was a mild stable hematoma of the transverse mesocolon and of the retroperitoneum. The descending thoracic aorta was examined and found free of dissection. His facial laceration was repaired; the fractured zygomatic arch was repaired after he recovered from thoracic surgery. He was noted to have transient cardiac muscle enzyme elevation during the first 4 postoperative days which returned to normal. He subsequently made an uneventful recovery.

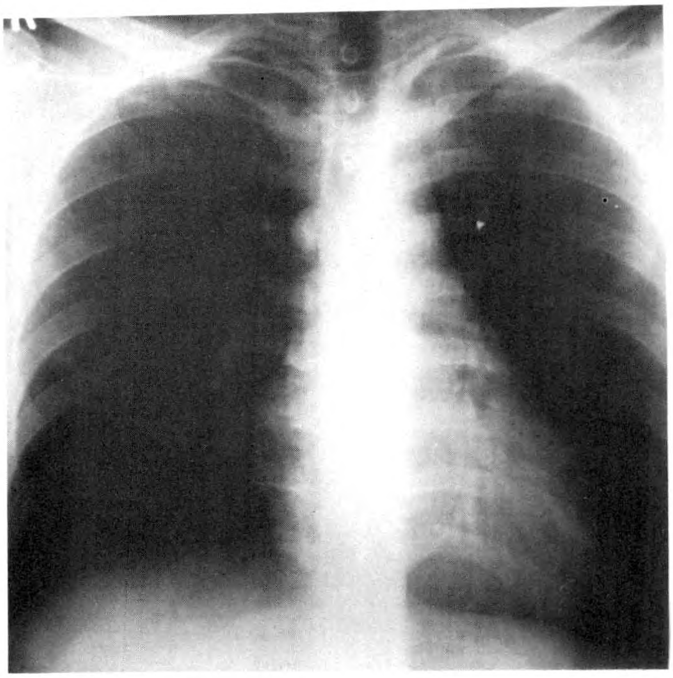

FIGURE 2.

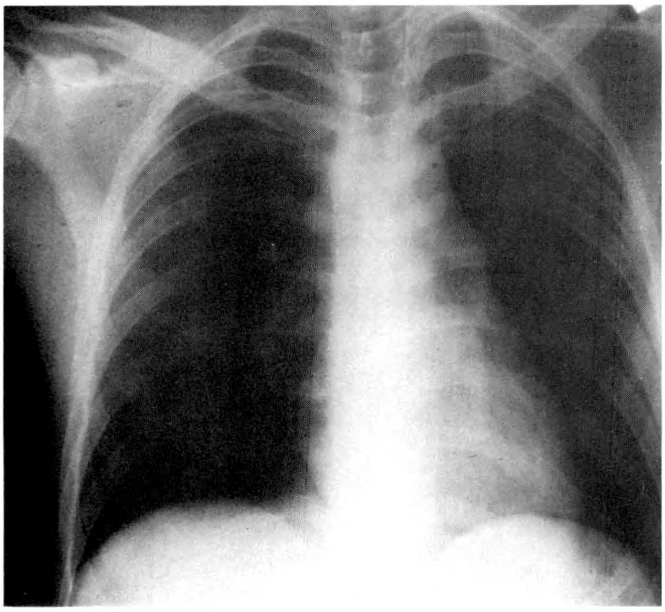

FIG. 1. A normal cardiac silhouette.

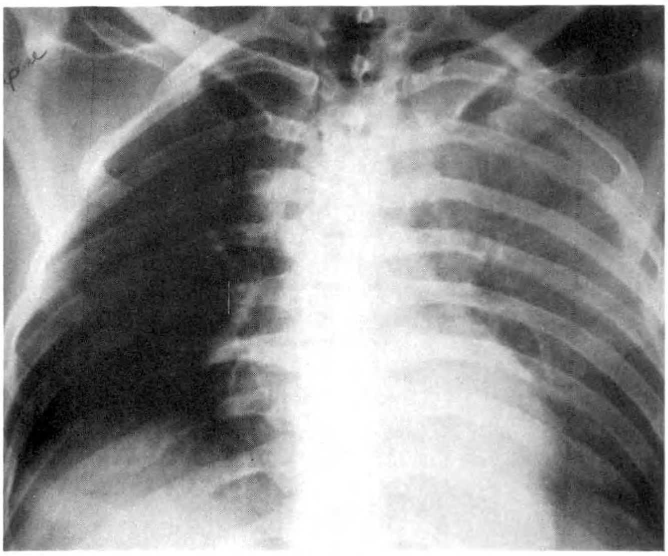

FIG. 3. Chest X-rays show left pleural effusion and suggestion of a wide mediastinum.

TABLE 1

	B/P Adm.	Cyonosis	CVP	Chest X-ray	Pericardiocentesis	Time to Surgery	Location of Tear	Type of Thoracotomy	Additional Injuries
Desforges[4] 1955	70/40	Yes	—	Right Hemothorax	No Rt. chest	9 hours	Right Atrium SVC	Right Thoracotomy	Fractured Left Femur
Bogidain[1] 1966	0/0	Yes	—	Multiple Rib Fxs. Enlarged Heart	Yes	Not Stated	Left Atrial Appendage	Left Thoracotomy	RLL Hematoma
Rotman[7] 1970	60/40	Yes	—	Not Done	No	Not Stated ? 1 hr.	Right Ventricle	Not Known	Traumatic VSD 10 days postop. Repaired 2 mos. later
Borja[2] 1970	60/40	Yes	—	Mediastinum Wide Hazy RLL	No	2 hrs.	Rt. Atrial appendage & lateral RA	Left thoracotomy Extended across sternum	Lacerations of knees
Noon[5] 1971	0/0	Yes	20	Multiple Rib Fxs.	Yes	Not Stated ? 1 hr.	LAA	Left thoracotomy Extended Across	Flail left Chest
	Not Known	Not Known	—	Left Hemothorax	No Lt. Chest Tube	2-3 hrs.	LAA	Left Thoracotomy	Depressed Skull Fracture
Siderys[8] 1971	0/0	Yes	35	Mediastinum Wide	Yes	Not Stated	Rt. Atrial Appendage	Median Sternotomy	None
SCVMC R.H.	0/0	Yes	25	Normal	Yes Bloody	1 Hour	Right Atrium IVC	Median Sternotomy	Facial Lacerations
T.A.	0/0	Yes	25–54	Normal	Trans. Abd. Bloody	4–5 hours	Rt. Atrial Appendage	Median Sternotomy	Fx. Lt. Lobe of Liver Compound Fx. Lt. Tibia, fibula
J.S.	70/30	Yes	14–20	Normal Heart Lt. Hemothorax	Yes Bloody	1 Hr.	Right Ventricle Out Flow	Median Sternotomy	Facial laceration & Fx. Zygoma Hematoma of Mesocolon

Discussion

Table 1 presents information obtained from the seven previously reported cases and our three cases. All of the published cases concerned young adults who had been involved in automobile accidents. All of these patients entered the emergency room in profound shock and were noted to be cyanotic in the trunk, neck and face. Many had distant heart sounds. Those in whom the central venous pressure (CVP) was measured had marked elevations. The chest x-rays were normal except in those in whom the pericardium was also ruptured. In those patients there was obvious hemothorax. Only one was noted to have an enlarged cardiac silhouette on chest x-ray. It is well known that acute pericardial effusions do not stretch the pericardium, but compress the heart, producing tamponade instead. Pericardiocentesis was diagnostic in six of this series and continued bleeding from the tube thoracotomy led to the diagnosis in three cases.

All but two patients in this series had atrial ruptures, which is what would be expected from Parnley's[6] series of post-mortem examinations. He reported a series of 546 cases of traumatic heart injury in which presumably 298 patients had ruptures into the pericardium. Of those in whom survival time was available 13 patients with atrial ruptures survived between 30 minutes and 3 days and only one with ventricular rupture survived longer than 30 minutes. Bright and Beck,[3] on the other hand, noted that 30 patients in their series survived longer than one hour, half were due to atrial rupture and half were ventricular ruptures. It is significant that the time between injury and operation was less than 5 hours in all of the reported surviving patients except the one reported by DesForges,[4] in whom the pericardium was torn, allowing decompression of any tamponade and where the tear apparently temporarily sealed and then rebled.

The right and left atrial appendages were the site of tear in six patients. This is presumably the weakest area and certainly the thinnest portion of the heart. The etiology of the injury in these patients was undoubtedly a compression force and rupture of the thin area. In three patients there was a tear at the junction of the atrium with the inferior or superior vena cava. In those instances the rapid movement of the heart into the left chest coupled with the compression force, presumably led to tear in the relatively fixed superior and inferior vena caval junction.

The type of thoracotomy incision is of great importance as demonstrated by a fourth case (not reported), in which the right atrial region could not be examined adequately through the left thoracotomy. The tamponade was released but the patient drained an additional two liters of blood postoperatively and may have represented a missed right atrial rupture which spontaneously sealed. If there is an associated hemothorax, then the appropriate chest may be opened. Otherwise a median sternotomy offers the superior exposure of both right and left atrium and is better tolerated by the patient. It is also easily extended into the abdomen for exploration of associated injuries.

A great deal of credit for the early identification of these injuries is due to the routine use of CVP catheters in all patients with severe trauma admitted to emergency room. The combination of shock with high central venous pressure in a patient with blunt chest injury can mean only tamponade or, less likely, a superior vena cava syndrome due to injury and bleeding from the great vessels. One must, of course, be certain of the position of the catheter tip. In our second patient the central venous pressure catheter was noted to be not quite in the superior vena cava and the high reading was therefore missed temporarily.

Cyanosis is not usually believed to be a symptom of tamponade. On the other hand, traumatic asphyxia is noted to be a cyanotic condition limited to the chest, neck and face but is usually associated with multiple petechial hemorrhages in this same distribution. Traumatic asphyxia is, of course, produced by sudden compression of the abdomen and lower chest producing a sudden rise in venous pressure of the chest, neck, face and lungs. A cardiac rupture in these instances may have protected the venous system and the tamponade simply produced a more chronic venous pressure elevation.

Summary

Blunt traumatic injuries of the heart are not uncommon. Chamber rupture into the pericardium, as evidenced by autopsy series, is one of the common injuries in severe blunt chest trauma. There is often a delay of at least 1 to 3 hours between injury and death in these instances. We have reported two cases of right atrial rupture, and one of right ventricular rupture which were surgically corrected, and have reviewed seven previously reported successful cases. With the early use of central venous catheter in the resuscitation of severely traumatized patients and suspicion aroused by finding of cyanosis in the upper one half of the body, this condition will be more readily and earlier diagnosed. Median sternotomy is the superior approach to these lesions.

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Diverticular Disease in the Transposed Colon Used for Esophagoplasty:

Report of Two Cases

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Diverticular disease of the colon is found more frequently in patients over 50 years of age. It is believed that about 10% of the population over 40 have diverticular disease. Welch reviewed over 2,000 X-rays and found the disease to be practically non-existent in those under 35, and that 2/3 of those in their eighties had the disease. The frequency of the inflammatory process also increased with age: thus in the sixties, about 1/5 of the patients with diverticulosis showed signs of diverticulitis while the incidence was 1/3 in those in their eighties.

If diverticulosis occurs in the colon in its normal habitat with the frequency ascribed, we would expect the same thing to occur when it is moved from the abdomen to the thorax as in instances of esophagocoloplasty. At present the colon is frequently used to reestablish alimentary continuity after total or subtotal esophagectomy because of cancer of the middle third or of the junction of the upper and middle third of the esophagus or because of extensive fibrosis due to lye ingestion.

Despite the use of esophagocoloplasty throughout the world, (several hundred published cases), we did not find any mention of diverticulosis in this connection. Up to the present, our experience with esophagocoloplasty consists of 93 cases: 75 operations were on patients with caustic stenosis of the esophagus; 16 on patients with cancer of the esophagus and two on patients with extensive stenosis of the esophagus secondary to operations on the esophagus. We had the opportunity of observing two instances of diverticulosis in the transposed colon among these patients. The appearance of the diverticulosis coincided with the appearance of dysphagia.

Case Reports

Case 1. E. R. A 50-year-old, white, Swiss, married man was first seen on August 4, 1965. There was a 1 year history of epigastric pain after swallowing cold liquids and dysphagia for solids, with a 13 Kg. weight loss. An X-ray of the esophagus showed an extensive cancer of the junction of the middle and lower third of the esophagus. The patient was operated on August 9, 1965. The operation consisted of a partial esophagogastrectomy with high esophagogastric anastomosis through a right thoraco-laparotomy approach according to Nakayama's technic.

There were no postoperative complications and the patient was able to swallow food well. He gained 8 Kg.

On January 14, 1966, he was seen again because of dysphagia. An X-ray of the esophagus showed partial stenosis of the esophagogastric anastomosis. Dilatations with Hurst sounds provided temporary relief but he returned on May 25 because of recurrence of dysphagia. An esophagoscopy and biopsy showed a recurrence of the tumor at the level of the anastomosis. Microscopic examination revealed adenocarcinoma.

On June 15, 1966, the patient underwent a subtotal esophagectomy and the gastrectomy was extended. The alimentary tract was refashioned by esophagocoloplasty. The transverse colon and a segment of the ascending and descending colon were used. Diverticulosis in this intestinal segment was not seen at operation. An opaque enema after operation showed the presence of some diverticula in the ascending and sigmoid colon (Fig. 1).

On August 7, 1967, the patient returned complaining of epigastric and left flank pain and nausea especially in the intervals between meals. Alkalies improved the pain. An X-ray of the stomach showed marked gastric stasis, 9 hours after swallowing the contrast. No ulcer was visible.

Since the patient continued to feel pain, he was reoperated on

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October 20, 1967. A supra-umbilical median laparotomy was performed and a peptic ulcer of about 2 cm. in diameter was found in the colon next to the cologastric anastomosis. A segment of about 2 cm. of colon and about 2 cm. of stomach were resected. Alimentary continuity was re-established by a new end-to-end anastomosis. Pyloroplasty was also done.

The patient was well, without pain and able to swallow food well. On August 27, 1968, he returned complaining of occasional dysphagia for solids and liquids. An X-ray of the transposed colon revealed the presence of large diverticula in this intestinal segment (Fig. 2). The patient had dilatations with the Hurst sound and his swallowing improved. He returned occasionally to the endoscopist for dilatations during that year and beginning of the next, because the dysphagia returned after a few months.

At the end of April 1969, he was seen again because of pain in the upper quadrants and weight loss. Palpation of the epigastrium showed a fixed tumor mass in the epigastrium next to the left costal margin. A new operation was performed on May 9, 1969. At laparotomy a neoplasm was found in the body of the stomach, attaching this organ to the posterior abdominal wall. An attempt was made to dissect the tumor but it was impossible since it involved the colon, the kidneys and the posterior abdominal wall. The patient died of cachexia about 20 days later.

Case 2. R. K. J.—RG 749970. An unmarried, white, Brazilian woman swallowed lye on November 20, 1964 and was treated clinically. A chest X-ray taken on December 31, 1964, showed perforation of the middle third of the esophagus and pleural effusion on the right. The pleural cavity and posterior mediastinum were drained. Due to extensive esophageal and pyloric stenosis the patient underwent operation on January 28, 1965. A cervical esophagostomy including closure of the distal part, gastroenteroanastomosis and closure of the cardia, gastrostomy and tracheostomy were done. The patient progressed satisfactorily and underwent dilatations of the cervical esophagus through the esophagostomy which elicited metallic sounds.

An esophagoplasty was done on December 1, 1965 and the patient was discharged on December 16, 1965, in good health. Stenosis was observed in the proximal anastomosis. Operation for correction of the stenosis was done on January 4, 1966. A good result was obtained and she was able to swallow food well. However, there was always plenty of reflux especially at night in the horizontal decubitus position.

On November 3, 1969, an X-ray revealed the presence of large diverticula in all the transplanted colon. Transit was slow. The cologastric anastomosis functioned well. The patient continued to have occasional dysphagia. On some days she was able to swallow normally and on others it was impossible. There were sporadic bouts of high fever (38–39°) preceded by chills. On July 10, 1970, a new X-ray showed diverticular expansion at the level of the sternal notch with the characteristics of Zenker's diverticulum (Fig. 3), a supraphrenic diverticular pouch and slow transit through the transplanted colon. The mouth of the cologastric anastomosis was ample. Signs of moderate chronic aspiration bronchopneumonia developed (Fig. 4).

Because of the persistent symptoms, the intensification of the dysphagia and the formation of the diverticula, we considered using the operation proposed by Reilly for the treatment of diverticular disease of the colon in its natural habitat. This operation was performed in February 1971. By means of a left cervical incision, a strip of muscle 2.5 cm. in diameter was removed from the colon along its length in the cervical region. The patient had a

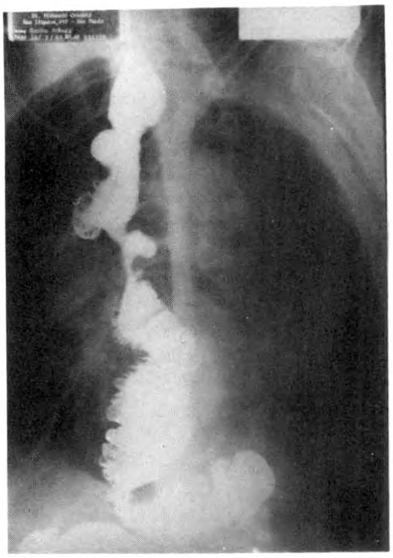

FIG. 2. X-ray of the transposed colon of Case 1, showing large diverticula in this intestinal segment.

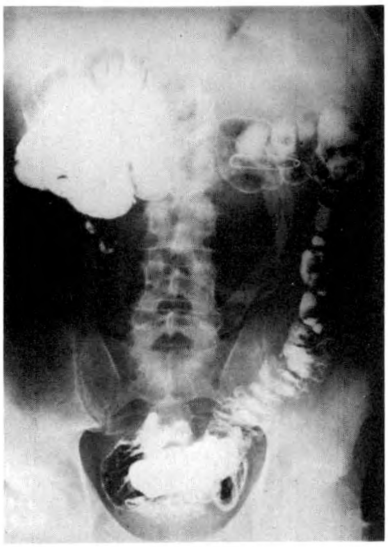

FIG. 1. Barium enema of Case 1, after esophagocoloplasty, showing some diverticula in the ascending and sigmoid colon.

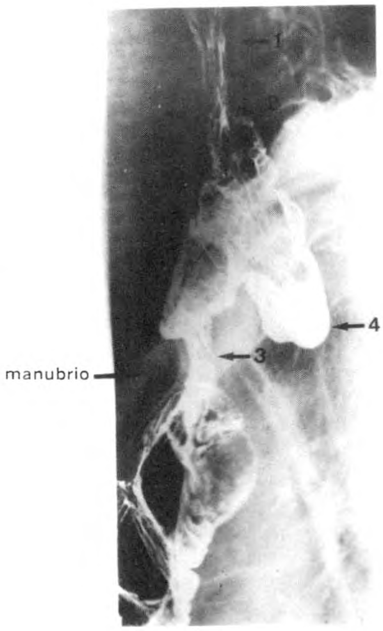

FIG. 3. X-ray of the transposed colon of Case 2, showing diverticular expansion at the level of the sternal notch.

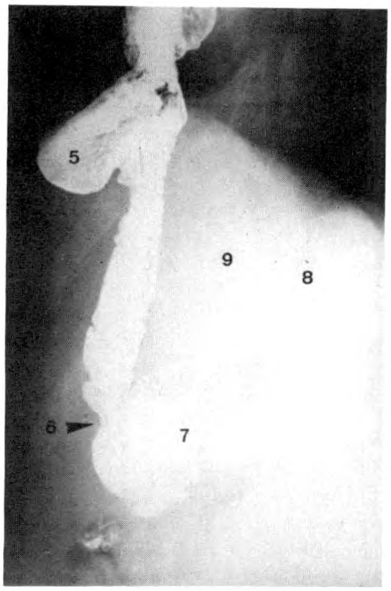

FIG. 4. X-ray of the transposed colon of Case 2, showing a supraphrenic diverticular pouch. Cologastric anastomosis is ample.

good postoperative recovery. The dysphagia and regurgitation disappeared.

A postoperative X-ray showed the cervical diverticulum seen on the previous examination to have disappeared. The epiphrenic diverticulum was still present. Transit across the transplanted colon improved considerably (Fig. 5). An opaque enema performed on this occasion did not show diverticula in the remaining abdominal colon (Fig. 6).

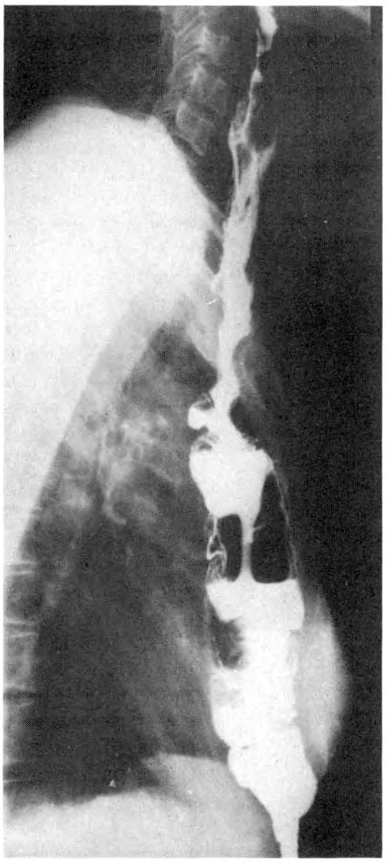

FIG. 5. X-ray of the transposed colon of Case 2, after Reilly's operation had been performed, showing disappearance of the cervical diverticula. Epiphrenic diverticulum is still present.

Discussion

As we can see on the first patient's X-ray, at the time of esophagocoloplasty, rare diverticula were present; one in the right colon and two or three in the left. The second patient did not have any diverticula.

The exact mechanism by which diverticula occur is still not understood. Since diverticula are more common in older individuals, it was thought that they were due to weakening of the colon's walls because of age. However, histological studies did not show muscular weakness in the elderly patients without diverticula.

Graser (1899),[4] was the first to describe the anatomy and pathogenesis of diverticula of the colon. He stated that they were consequences of weakness of the intestinal wall at the areas of vascular penetration. He demonstrated, experimentally, the direct relationship between diverticula and the blood vessels. He believed that an increase in the intracolonic pressure was necessary to start the appearance of the diverticula. This pressure would be provided by constipation.

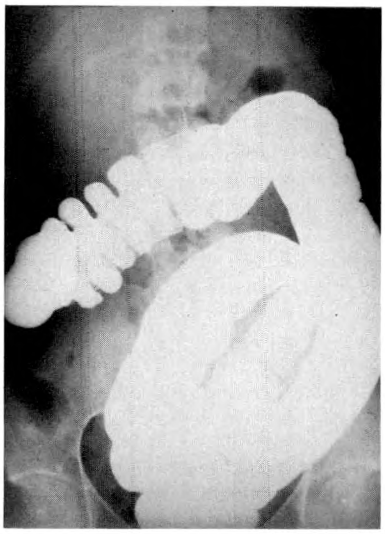

FIG. 6. Barium enema of Case 2 showing no colonic diverticula.

Keith (1910),[5] introduced the theory of muscular spasm which would give rise to an irregular uncoordinated and persistent contraction of the affected colonic segment. This contraction would narrow and shorten the colon so that it would assume the shape of a rigid tube. The increase in muscular pressure would produce the mucosal herniations at the points of least resistance represented by penetration of the vessels.

Edwards (1934),[2] believed that muscular spasm was responsible for the appearance of the diverticula; he called our attention to the thickening of the muscular layer, considering it hypertrophic and previous to the onset of the diverticula.

Arfwiddson (1964)[1] and Painter (1963–1964),[6,7] recorded the motility of the colon in normal individuals and in patients with diverticular disease. They found that under resting conditions, the intracolonic pressure tracings were similar in both groups. However, when the diseased colon is stimulated by ingestion of food, or injections of morphine, prostigmine, or by emotion, more frequent and higher intraluminal pressures are produced than in normal individuals.

Simultaneous cineradiography and pressure recording has shown that the colon produces these pressures by segmenting so that it acts as a series of "little bladders", whose outflow is obstructed at both ends by contraction rings and in which high pressures may be localized (Painter *et al.* 1965).[8] Segmentation is concerned in the transportation and halting of the colonic contents and it appears that it is responsible for the pulsion force that causes diverticula. The presence of diverticula is almost certainly caused by abnormal activity of the colonic musculature that causes excess intracolonic pressure.

The cause of this primary abnormal activity is not well known. According to Grace (1951),[3] emotional factors have a great influence on the activity of the colonic muscles. Under emotional stress he observed contraction of the longitudinal muscles with shortening of the bowel, as well as an increase in the activity of the circular muscles.

We believe that emotional factors played a part in the genesis of the diverticula in both these patients, for they were highly emotional. The second patient due to her emotional problems, attempted suicide by swallowing lye, the cause of the stenosis.

In patients who undergo esophagocoloplasty, the food descends the colon by gravity, so that contractions are not caused in the interposed colon. As has been pointed out by Sieber and Sieber,[12] in cineradiographic study of motility, peristaltic contractions are almost absent in the interposed colon. We also confirmed this finding in a study of the motility of the interposed colon in some of our patients (Fig. 7). Since the food descends by gravity it takes a little longer to reach the stomach than in individuals with a normal esophagus. As we have mentioned, in both our patients we used a loop of colon in an isoperistaltic direction.

The study of the motility of the transplanted colon was done on the first patient. A tracing was not obtained on the second patient because it was impossible to introduce the polyethylene tube into the colon. The study of the motility showed identical changes to those already seen in patients with diverticular disease of the colon; that is, an increase in the intraluminal pressures with more frequent and high amplitude contractions (Fig. 8). Since this intestinal segment now functioned as an esophagus the continuous ingestion of saliva and food constituted a permanent stimulus for its contraction and the consequent increase in the intraluminal pressure may have caused the appearance and growth of the diverticula in a short length of time. In our patients, the diverticula attained a size shown in the X-ray two years postoperatively, which is an uncommon observation in diverticular disease of the colon. We postulate that the continuous and permanent stimulus of swallowing may have acted in the same manner that Painter and Painter *et al.*[6,7,8] observed in the reaction of the colon when stimulated by morphine.

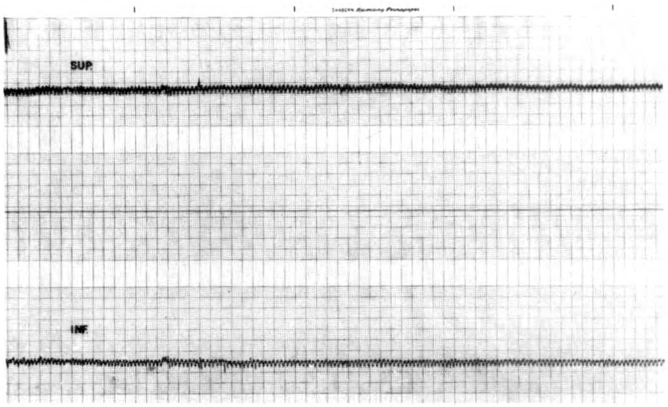

FIG. 7. Motility record of the transposed colon in a patient submitted to esophagoplasty who is clinically well. The two tips are 10 cm. apart. During swallowing, waves were recorded.

The first patient was treated with antispasmodics and dilatation of the colon with Hurst sounds. He died about a year after the appearance of the diverticula, in consequence with the recurrent cancer. We were more concerned about the second patient because of her youth. Her disease was not cancer of the esophagus but stenosis resulting from swallowing lye. The patient's difficulty in swallowing as well as the episodes of regurgitation which caused aspiration into the bronchial tree, led us to consider the possibility of removing the colon from the anterior mediastinum. Since the patient had already undergone gastrectomy, we abandoned the idea because it was not possible to bring the stomach up to the cervical region. It was then that we considered

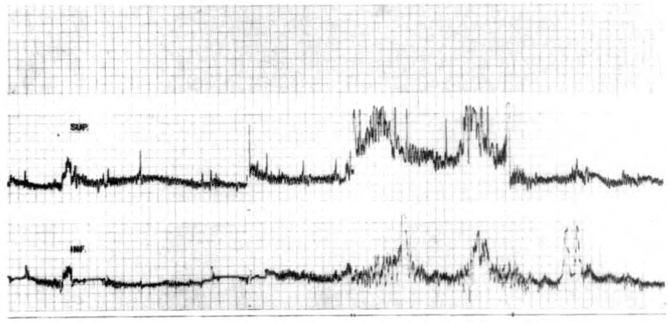

FIG. 8. Motility record of the transposed colon of Case 1. There are a great number of waves of high amplitude and long duration.

the use of Reilly's operation which was recommended for diverticular disease of the colon; that is, to resect a band of intestinal musculature. We decided to try this operation only on the cervical segment, and observe the results. If necessary, we thought we would do a sternotomy at a second stage and continue the operation along the length of the colon up to the anastomosis with the stomach. The patient improved so much with the muscular resection of only this segment that a second stage has not been necessary, thus far.

Studying these two patients, we concluded that esophagoplasty should not be done when the patient has diverticulosis of the colon, regardless of the location and even if there are few diverticula. In these instances we recommend that the alimentary continuity be reestablished by using the stomach, mobilizing it to the thorax and placing it in the substernal space. However, if a segment of colon is used in a patient who does not have diverticulosis but later develops the disease, Reilly's operation should be considered as the result was excellent. When diverticula are found in a patient in whom the colon is being transposed and there is no possibility of using any other organ to re-establish alimentary continuity, we believe it should be convenient to resect a muscular band along the length of the antimesenteric taenia at the same time that esophagocoloplasty is done. This procedure might avoid a future sternotomy in order to expose the colon and perform this operation.

Cases similar to ours are not found in the literature, perhaps, because the greatest number of esophagocoloplasty procedures have been done on patients with cancer of the esophagus. Usually these are patients more than 50 years of age who have a greater chance of having postoperative diverticular disease, but they do not survive a sufficient period for this to happen. Patients with caustic stenosis of the esophagus who undergo esophagocoloplasty are usually under 40 and therefore are less apt to develop diverticular disease of the colon.

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Response of the Interposed Human Colonic Segment to an Acid Challenge

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THE OPERATIVE TREATMENT FOR benign stricture of the esophagus should result in unobstructed passage of food and prevent acid reflux with recurrent stricture formation. If the stricture is far advanced and cannot be satisfactorily treated by dilatation and an antireflux operation, esophageal resection with interposition of the colon between the esophagus and stomach has been proposed. We have performed 19 such operations for benign disease without hospital mortality or major complications which demonstrates the feasibility and safety of this approach. However, others have objected to the lack of peristalsis in the colonic segment and failure to participate in the swallowing process.[1,4]

In the present study, patients who have undergone colonic interposition for benign stricture of the esophagus have been evaluated by cinefluoroscopic, and manometric testing with special emphasis on the response of the interposed colon to an acid stimulus.

Clinical Material

Nine patients were studied from 1 to 26 months following colonic interposition for benign stricture of the esophagus (Table 1). Patients ranged in age from 27 to 80 years. In five patients, multiple operative procedures had been performed previously, with poor results each time. In three patients, the interposition operation was performed as an emergency procedure; two for perforation at the time of esophageal dilatation and one for uncontrollable bleeding from erosive esophagitis. In all patients, the isoperistaltic left colon based on the left colic vessels was used. The colonic segment extended from just below the aortic arch to the posterior wall of the stomach at the junction of its proximal and middle third. The follow-up period ranged from 2 months to 2 years in the nine patients.

Methods of Study

Manometry. Three polyvinyl catheters (ID 0.034 in.) were bonded together with open tips spaced 5 cm. apart. This assembly was passed through the nose of fasting patients into the distal colon, and positioned just above the diaphragm under fluoroscopic guidance. The tube could not be passed into the stomach in any of the nine patients. The catheters were filled with distilled water and connected via a pressure transducer to a Sanborn direct writing multi-channel recorder. Small volumes of distilled water were infused continuously at a rate insufficient to produce a pressure elevation in the system (0.076 ml./min./tube).

Activity in the resting colon was observed for periods ranging from 5 to 30 minutes. The duration of colonic contraction was recorded as the average duration of the peristaltic waves recorded by the three polyvinyl tips. Following this period of spontaneous activity a 30 cc. bolus of distilled water was injected into the colonic segment either through the middle or distal tip and colonic peristaltic activity recorded. In order to test the sensitivity of the interposed colon to the presence of acid, manometric studies were performed during and

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TABLE 1. *Resection and Colon Interposition for Benign Stricture of the Esophagus*

Patient	Previous Operation	Pathology	Operation	Result
Case 1 64, M	None	2 cm stricture, distal esophagus, hiatal hernia	Left colon interposition	Swallowing satisfactorily
Case 2 70, M	1) Esophagomyotomy 2) Cardioplasty	Stricture with full thickness destruction of esophagus	Left colon interposition	Swallowing satisfactorily. Died 7 mos. p.o. from chronic lung disease
Case 3 27, M	None	Stricture above E-6 junction	Left and transverse colon interposition	Swallowing satisfactorily
Case 4 53, M	Hiatal hernia repair Vagotomy and Pyloroplasty	Short stricture 6 cm above diaphragm Hiatal Hernia	Left colon interposition	Swallowing satisfactorily
Case 5 57, F	Three hiatal hernia repairs, partial gastrectomy	Short stricture distal esophagus, hiatal hernia	Left colon interposition	Swallowing satisfactorily
Case 6 46, M	2 Cardioplasties Fundic patch operation	Bleeding esophagitis, short stricture at E-6 junction	Left colon interposition	Swallowing satisfactorily, mild symptoms of reflux
Case 7 80, F	Two hiatal hernia repairs, esophagomyotomy, fundic patch operation, 40% gastrectomy	Severe esophagitis	Left colon interposition	Swallowing satisfactorily; alkaline esophagitis
Case 8 37, F	None	Long stricture distal esophagus	Left colon interposition	Swallowing satisfactorily
Case 9 55, M	None	Stricture distal ⅓ esophagus, obstructing antral ulcer	Antrectomy with left colon interposition	Swallowing satisfactorily

following the injection of a 30 cc. bolus of 0.1 N HCl acid. The esophageal-colonic junction was determined by withdrawing the assembly with the patient swallowing at regular intervals, and noting the level at which esophageal peristalsis was observed.

pH Recording. With the triple lumen tube placed at the level of the diaphragm, a long Beckman pH electrode (No. 39042) was passed into the colon and was placed at the distal tip of the polyvinyl tube. The resting pH in the supradiaphragmatic colon was recorded. Colonic acid clearing was evaluated after injection of a 30 cc. bolus of 0.1 N HCl acid into the distal colon. The pH electrode was then withdrawn slowly up the colon segment into the esophagus and pH recorded at one cm. increments.

Cinefluoroscopy. Cinefluoroscopy was performed on all patients, initially in the supine, and later in both erect and supine positions.

Results

Eight of the nine patients are eating and swallowing satisfactorily 3 months to 2½ years following operation. One patient, Case 6, has symptoms of reflux relieved by antacids. Esophagoscopy in this patient was unremarkable with no gross evidence of esophagitis. One patient died 7 months following operation for chronic obstructive pulmonary disease, but was swallowing without difficulty prior to death.

The resting supradiaphragmatic colonic pH averaged 7.2 in eight patients. Spontaneous colonic peristalsis was observed in three of nine patients, occurring at an average frequency of one contraction every 4 to 6 minutes. The peristaltic waves occurred in a progressive pattern down the colonic segment at an average rate of 1.0 cm./sec. In six patients, spontaneous colonic activity was absent during an average observation period of 18 minutes. In the three patients which demonstrated spontaneous colonic peristalsis, the average amplitude of contraction was 14, 26, and 23 mm. Hg. The duration of colonic contraction was 72, 61, and 34 seconds (Fig. 1).

Colonic response to a 30 cc. bolus of distilled water was observed in seven patients. There was no response in three patients. In four patients, colonic contractions occurred within 4 minutes at a frequency of one contraction every 2 to 4 minutes. The average amplitude of colonic contraction was 18 mm. Hg with a range of 13 to 22 mm. Hg. The average duration of peristaltic contraction was 48 seconds with a range of 16–93 seconds.

When 0.1 N HCl acid was instilled into the distal

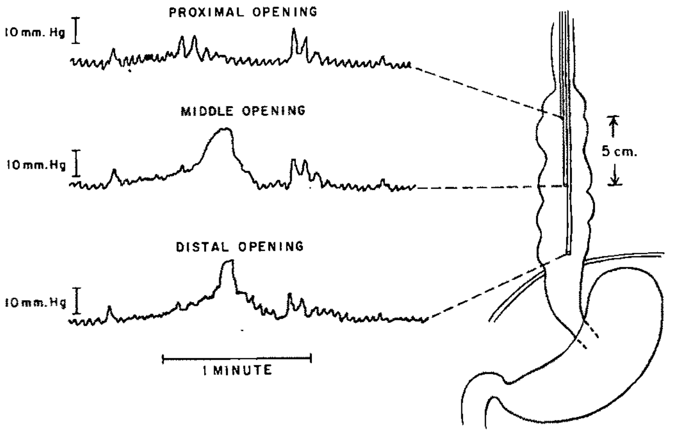

FIG. 1. Spontaneous peristalsis in the interposed colonic segment. Pressures recorded at three levels (Case 6).

colon, there was a colonic peristaltic contraction within 2 minutes in all nine patients. The average interval between injection and response was 56 seconds. The frequency of contraction was variable with a range of two contractions every 1 to 8 minutes. The average amplitude of colonic contraction was 19 mm. Hg with a range of 10 to 30 mm. Hg. The average duration of colonic contraction was 45 seconds with a range of 25 to 80 seconds (Fig. 2).

Acid clearing from the colonic segment was determined in eight patients. The bolus of acid was completely cleared in seven patients, and one patient failed to clear the acid over a 2-hour period. The average time required to clear the acid was 2 minutes with a range of 1 to 6 minutes (Table 2). Reflux of the acid from the stomach into the supradiaphragmatic colon was not detected.

Cinefluoroscopy. There was agreement between this study and reflux testing in that no reflux of contrast material was demonstrated from the stomach into the colon or from the colon into the esophagus. No active peristalsis of the colon was observed and the barium emptied readily from the colon into the stomach by gravity in the standing position only.

Discussion

There has been lack of agreement as to how to restore functional continuity of the upper GI tract following resection of esophageal strictures. Anatomically, the stomach is easiest to use but its use is besieged with a high incidence of recurrent reflux esophagitis, pneumonitis, and stricture formation.[5] The use of the colon has not gained universal approval because of its assumed passiveness in the swallowing process and the lack of evidence regarding the colonic segment's role in preventing the injurious effects of acid reflux.

The present study has shown that spontaneous colonic peristalsis occurred in one-third of our patients. When 0.1 N HCl acid was used as a stimulus, peristalsis occurred in every patient. The amplitude and duration of colonic contraction after acid was similar to that ocurring spontaneously and after a water bolus. Thus, it would appear that there is an intrinsic, reproducible colonic peristaltic response of approximately 18 to 21 mm. Hg amplitude, lasting 45 to 56 seconds, progressing at a rate of 1.0 cm./sec. which may occur spontaneously, after water, and particularly after acid stimulation. Of the four patients who lacked spontaneous colonic activity, three also failed to respond to a water bolus, but all of them responded to an acid load. It may be this striking sensitivity to the presence of acid which stimulates the colon to empty its contents and prevent injury to the normal esophagus above.

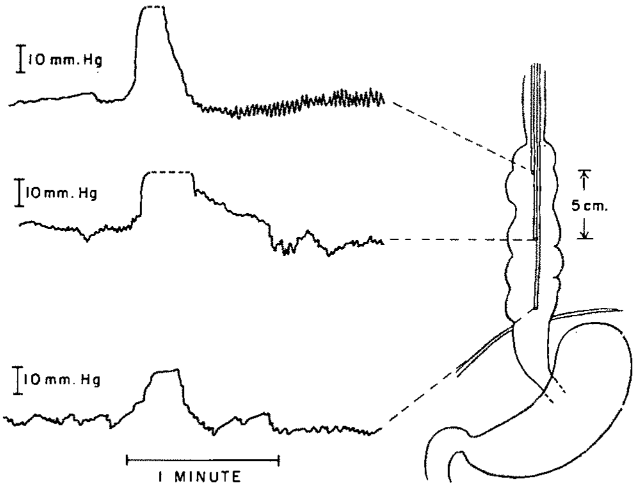

FIG. 2. Colonic response to 0.1 N HCl acid bolus. Onset of contractions 2 seconds after instillation of acid.

The resting supradiaphragmatic colonic pH was neutral or near so, averaging 7.2 in nine patients. No patient showed evidence of reflux of gastric acid into the distal colon at any time during the study.

The clearing of acid from the colon was measured in a manner similar to tests developed for the detection of esophagitis in patients with reflux with or without hiatal hernia.[2,6] The average time for acid clearing from the colon was 2 minutes in seven of eight patients tested. Although acid clearing from the colon cannot be correlated with swallowing as has been done in the esoph-

TABLE 2. *Colonic Response to 30 CC 0.1 N HCl Acid*

Case	Frequency of Contraction	Amplitude of Contraction	Duration of Contraction	Reflux	Acid Clearing	Interval Between Injection & Response
1	1 in 2 min.	18 mm Hg	80 sec.	None	1 min.	55 sec.
2	1 in 2 min.	30 mm Hg	53 sec.	None	3 min.	immediate
3	2 in 1 min.	19 mm Hg	37 sec.	None	1 min.	40 sec.
4	1 in 1 min.	10 mm Hg	25 sec	None	—	110 sec.
5	2 in 2 min.	12 mm Hg	26 sec.	None	3 min.	60 sec.
6	3 in 8 min.	24 mm Hg	68 sec.	None	6 min.	40 sec.
7	4 in 15 min.	22 mm Hg	42 sec.	None	immediate	25 sec.
8	2 in 6 min.	25 mm Hg	25 sec.	None	immediate	50 sec.
9	3 in 6 min.	13 mm Hg	46 sec.	None	None	125 sec.

agus, all patients cleared acid within 6 minutes. In the one patient who failed to clear acid (Case 9), the interval between acid injection and colonic response was the longest (125 seconds), and was twice the average for the entire group. It is interesting that in this patient resting supradiaphragmatic colonic pH was the lowest of the nine patients and there was absence of spontaneous colonic peristalsis and no peristalsis after a water load. This retarded response may have been due to the fact that the patient was studied only 13 days after operation, and a relative "ileus" may have been present with failure to clear the acid.

An important function of any esophageal substitute is that it protects the proximal esophagus above the anastomosis. This was true for four of the six patients tested in that esophageal pH following an acid load into the distal colon was 6.0 or above. This protection probably occurs by the spatial separation between stomach and esophagus, but might occur by active colonic contraction in response to acid with prompt return of the acid into the stomach. The colon is known to secrete bicarbonate and colonic secretions could act as a buffer to any acid which might reflux into the distal colon. The latter would explain the immediate colonic acid clearing seen in two patients.

It has been stated that the only peristaltic activity in the interposed colon is that of the gastrocolic or mass action type of reflex occurring 3 to 4 times daily.[1,4] Our observations indicate that colonic contractions occur more frequently than previously thought and are of the type II contractions with an amplitude of 15 to 40 mm. Hg., lasting 25 to 30 seconds as described previously by Laurens and Hightower[3] for the colon in normal position. Whether these peristaltic waves are effective in propulsion of food from proximal esophagus to stomach, cannot be concluded from these studies.

Summary

Nine patients having esophageal resection and colonic interposition for benign disease have been evaluated clinically, with pH reflux testing, acid clearing, manometric, and cinefluoroscopic technics. All patients are swallowing well after operation and eight of the nine are completely satisfied with the operative results.

One third of the patients showed progressive spontaneous peristalsis. Stimulation of the colonic segment with water, and particularly with acid, caused a reproducible colonic contraction, and was comparable to the type II colonic contraction described previously for the colon in normal position. The colonic response to an acid stimulus was the most consistent, occurring in all nine patients. Because of this sensitivity to acid, it is proposed that the interposed colon acts as a protective barrier, and any acid which refluxes is either buffered immediately by alkaline colonic secretions or induces colonic peristalsis with eventual return of the acid into the stomach.

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Arteriovenous Malformations of the Scalp

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ARTERIOVENOUS MALFORMATIONS (AVMs) of the scalp, though rare, present an interesting challenge to he surgeon. Their basic etiology is not clear. They nay result in complex derangements of cerebral hemo-lynamics, and their surgical treatment can be extremely lifficult.

The purpose of this report, in addition to the pre-entation of six illustrative cases selected from a series f 10 patients, with 20 years' follow-up in two, is to liscuss the causes of this abnormality, its incidence, and ther important characteristics which are not available in the literature. It is based on review of 148 cases reported in the literature and the present series of 10 patients.

Case Reports

Group One: Patients with no history of trauma and no irth-mark.

Case 1. A 32-year-old man noticed a mass in the mid-frontal egion behind the hairline 2 years prior to admission. He com-lained of no headaches; however, nervous excitement caused ortuosity and enlargement of the mass which was associated vith throbbing and tenderness. Physical examination showed a ound, irregular and pulsating mass in the midline, anterior to the oronal suture. It measured 5 cm. in diameter and 1.5 cm. in eight.

The right internal carotid angiogram revealed no abnormality. he right superficial temporal angiogram showed moderate dila-ation of this artery and its frontal branch with a serpiginous ollection of moderately dilated vessels in the region of the regma. There was no evidence of connection between the di-ated superficial vessels and the cerebral vasculature.

The entire mass was removed following ligation of the feeding essels. Twenty years later, the patient remains well with no ign of recurrence.

Case 2. A 44-year-old woman was admitted for the third time because of scalp bleeding. The patient's history dated back to the age of 18 years when she noted a pulsating lump in the right parieto-occipital region. A partial excision of the lesion together with multiple ligation of the feeding arteries was carried out. She had no further severe bleeding until 23 years later when uncontrollable bleeding occurred. To stop the bleeding, the right common carotid artery was ligated and a partial excision of the recurrent AVM was performed. The bleeding, however, still remained troublesome. A left carotid angiogram revealed filling of the AVM. Thus, the left external carotid was ligated. She had several skin grafts in the occipital region and on one occasion she developed osteomyelitis of the skull. The patient was finally discharged after 8 months of hospitalization with some improvement.

She was readmitted 8 months later because of bleeding, and the AVM was injected with sclerosing solution.

At the present time the patient is well except for the occasional scalp bleeding which may be severe enough to require blood transfusion. Currently, she is receiving cobalt treatment for the remaining AVM in her hometown hospital.

Case 3. A 24-year-old woman was admitted because of blurred vision. Ten years previously the patient gradually developed loss of hair in the right parietal scalp, prominent vessels, headaches, and tinnitus. The diagnosis of a right parietal scalp AVM was made by carotid angiography and the right external carotid was ligated. A few months later, the tinnitus recurred and the vessels became dilated. Surgical procedures such as partial excision and ligation of the feeding arteries were carried out with little success. Later, she noted some visual blurring and examination revealed 4 diopters of papilledema bilaterally. Skull X-rays showed a thick calvarium with markedly accentuated vascular impressions. Angiography demonstrated a diffuse AVM of the right scalp which was supplied by the branches of the left external carotid and both vertebral arteries as well as the intracavernous branches of both carotid arteries. Lumbar puncture revealed clear cerebrospinal fluid with an opening pressure of 450 mm. H_2O, 12 mg./100 ml. protein, 65 mg./100 ml. sugar, 8 crenated red blood cells and no white blood cells.

After preparation of a large pedicle graft, a complete excision of the AVM together with the involved bone was attempted. Bleeding from the scalp and bone required repeated blood transfusions and was controlled with difficulty. Following operation her condition was satisfactory for a few days; however, later she developed signs of progression of the increased intracranial pressure and elevation of the skin graft. The patient was operated on

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again on the eighth postoperative day and a large epidural clot together with a very swollen brain were found. She did not respond to the treatment and died 8 weeks after excision of the AVM.

Group Two: Patients with no history of trauma but with birth-mark.

Case 1. A 31-year-old woman was born with port-wine stains on the right side of the head, ear, and cheek, in which area she gradually developed throbbing pain and pulsation. During her first pregnancy the symptoms became more severe with occasional bleeding so that it was terminated by Caesarian section in the seventh month due to fainting and bleeding episodes.

Following pregnancy, a right carotid angiogram showed an AVM in the distribution of the right external carotid artery. At operation, this artery was ligated and partial resection of the AVM was carried out with relative improvement. A month later, the symptoms recurred and gradually increased in severity. The right carotid angiogram was repeated which showed the remaining AVM. She was operated upon and partial excision was done. After a few years, the previous symptoms recurred and an angiogram showed that the AVM was fed by branches of the thyrocervical trunk. She was operated on for the third time and excision and multiple ligations were performed with relief of symptoms.

Group Three: Patients with history of trauma but no birth-mark.

Case 1. A 35-year-old man was stabbed in the left temple 15 years previously. He was taken to a local hospital and the wound was repaired. He subsequently noticed swelling and tenderness at the site of the stab wound and as time went by throbbing headaches and buzzing in the left ear developed. The physical examination revealed dilated and tortuous vessels over the entire scalp which were more prominent on the left side. A loud bruit was present in the left temporal area.

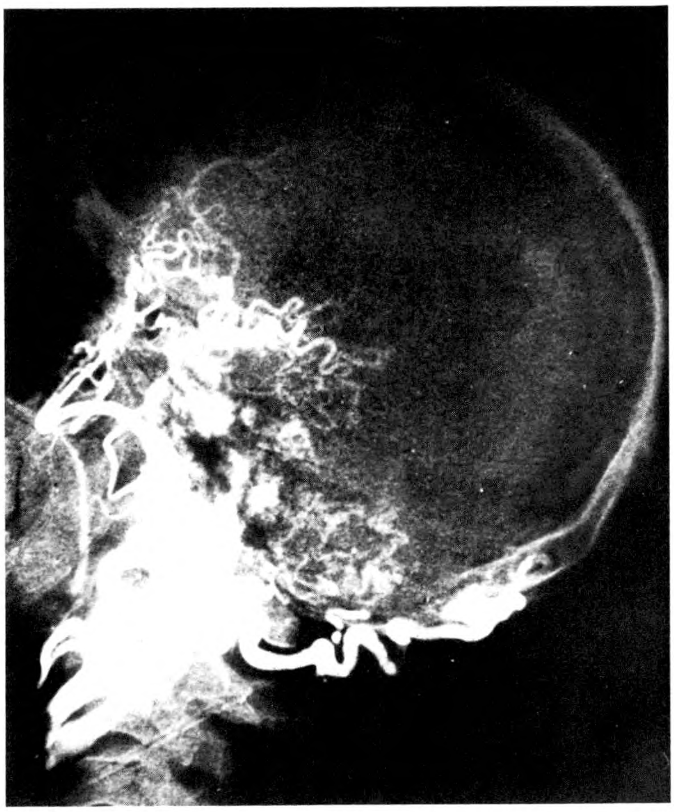

FIG. 1. An early phase of a left lateral carotid angiogram which shows dilatation of the occipital and internal axillary arteries. The superficial temporal artery which was interrupted at the time of injury is not seen in this phase.

Left internal and external carotid angiogram with subtraction films showed interruption of the superficial temporal artery at the level of the preauricular region with huge recurrent branches of the internal maxillary artery, posterior auricular artery and occipital artery draining into the preauricular region (Fig. 1). The left external jugular vein was extremely large and opacified early (Fig. 2). The arterial circulation time was 2¼ and the arteriovenous circulation time was 4¾ seconds.

The abnormal vessels in the left temporal region were removed in block following ligation of the external carotid artery. His symptoms were relieved after the operation. However, long-term follow-up was not available.

Group Four: Patients with history of trauma and birth-mark.

A 42-year-old man had multiple birth-marks on the left side of his body involving the temple, upper neck, buttock and the calf. At the age of 16 years, he was involved in a car accident and was injured about the left forehead. Following the accident he noticed throbbing in the left side of his head and gradually the vessels in this area became enlarged and distended. The physical examination revealed an area of port-wine discoloration together with an irregular pulsating mass in the left temporal region. Bruit was present and diminished by compression of the superficial temporal artery. In an operation the left external carotid artery was ligated and a partial excision of the lesion was carried out.

The patient was relatively symptom free for about 6 years, then the throbbing and swelling recurred. He was subjected to three operative procedures consisting of multiple ligations and excisions with some relief.

Terminology and Historical Background

Arteriovenous malformations have been termed: arteriovenous aneurysm,[29,37] cirsoid aneurysm, racemose aneurysm, aneurysm by anastomosis, plexiform angioma,[33] aneurysmal varix,[28] arteriovenous fistula,[13] abnormal arteriovenous communication,[37,38] and have been known for centuries.[48]

The Greek legend of the "Gorgons" head covered by snakes has been suggested by Vollmar and associates[48] as an early description of this disease. These authors also quoted a case of "Ranken angioma" from the sixteenth century for which surgical treatment was attempted.

During the latter part of the nineteenth century the presence of free communications between an artery and a vein was recognized and reports of traumatic arteriovenous malformations appeared in the literature.[26,51] The congenital form was not described until studies of the development of the vascular system in embryos were done during the early part of this century.[39] Some years later the pathology of the arteriovenous malformation was studied in more detail and it was shown that no capillary network exists between communicating arteries and veins.[25]

Etiology

Four major causes have been considered.

1. *Congenital AVMs*

Case reports such as that of Davies-Colley (Case 1)[10] or the Group Two patient of the present study in whom an AVM developed at the site of a red birthmark without any history of trauma may be considered congenital. Nevertheless, a congenital AVM may exist without any apparent local abnormality at birth, or a birthmark may be present without ever being manifested as an AVM.

Three explanations have been suggested for the development of congenital AVMs.

A. Persistence of the primitive arteriovenous communication and capillary agenesis.[20,28,53]

According to this theory, the development of the primitive arteriovenous communication into arteries, capillaries and veins at 4 weeks gestation (4 mm. embryo) fails to take place; instead, the embryonic plexus-like arteriovenous pattern without interposition of the capillary network is retained.

B. Hamartoma. Some authors believe that AVMs originate from vascular hamartomas.[50,52] Hamartomas are tumor-like, non-neoplastic lesions which are characterized by abnormal mixture of tissues indigenous to the part, with an excess of one or more.

C. Formation of a fistula at the site of arteriovenous crossing.[3,18] After most cranial arterial walls become thickened (40 mm. embryo) arteries and veins frequently cross and accompany each other. Since these vessels at the site of crossing are only separated by a double layer of endothelial cells, a fistula could develop and cause abnormally dilated vascular nets.

The concept of hamartoma seems to offer a better explanation for the common cause of AVMs than the persistence of primitive blood vessels or the formation of a fistula at the site of arteriovenous crossing. A hamartoma formed of primitive vascular plexus on the basis of a larger vascular bed may attract more blood than the normal primitive vascular plexus thus causing its own persistence and since there is no tissue to supply, capillaries do not develop and differentiation does not take place.

It is of note that direct arteriovenous communications are also found in blood vessel tumors such as hemangiomas[8,36] and in highly vascular neoplasms like hemangioblastomas,[35] meningiomas, gliomas and some of the metastatic tumors[12] where again a relative crowding of blood vessels and a larger vascular bed exists.

Activating factors of the congenital AVM: Symptomatic congenital AVMs are not common immediately after birth or during childhood. Most patients usually seek medical attention after the second decade. A few factors are said to be capable of establishing an active or perhaps more active blood circulation in the malformation and cause an asymptomatic AVM to become symptomatic. These include mechanical trauma, vasomotor disturbance, endocrine stimulation, and inflammation. Mechanical trauma including sneezing and parturition may cause a sudden increase in intravascular pressure and rupture the embryonic septum between the artery and the vein (the two layers of endothelial cells) and produce an arteriovenous fistula.[21] In vasomotor disturbance the increase of hemodynamic activity is considered the activating factor.[23] Whether or not inflammation and endocrine stimulation such as growth, puberty, menstruation, and pregnancy may also act by hemodynamic alteration is not clear.

2. *Traumatic AVMs*

Both penetrating and non-penetrating scalp injuries have been said to cause arteriovenous fistulae which gradually evolve into a malformation. Case reports such as that of Amyes and Courville[1] or group three patient of the present study in which an AVM developed at the site of a penetrating wound strongly suggest a traumatic origin. In cases of non-penetrating wounds, however, one cannot be certain about the trauma being the cause of the lesion, since scalp injuries may also activate a silent and unrecognized congenital AVM or be incidental. On this basis, some of the cases reported in the literature as traumatic in origin may not be so.

A non-penetrating scalp wound which causes an AVM may damage the walls of an artery and a vein in apposition, and produce a fistula which enlarges due to shunting a high pressure arterial blood into a low pressure venous system.

In addition to the scalp injuries received during childhood or later in life, trauma and pressure exerted on the scalp at childbirth have been also considered a possible origin of traumatic scalp AVM.[38] This kind of lesion may be confused with true congenital AVM.

3. *AVMs Caused by Infection and Inflammation*

Although primary arterial disease, ulceration and infection are considered rare causes of arteriovenous fistulae we have not found a reported case of this kind of AVM involving the scalp.

4. *Familial AVM*

Familial scalp AVM seems to be extremely rare. We had the opportunity to observe this condition in a Persian family.[19] To our knowledge, no similar example has been

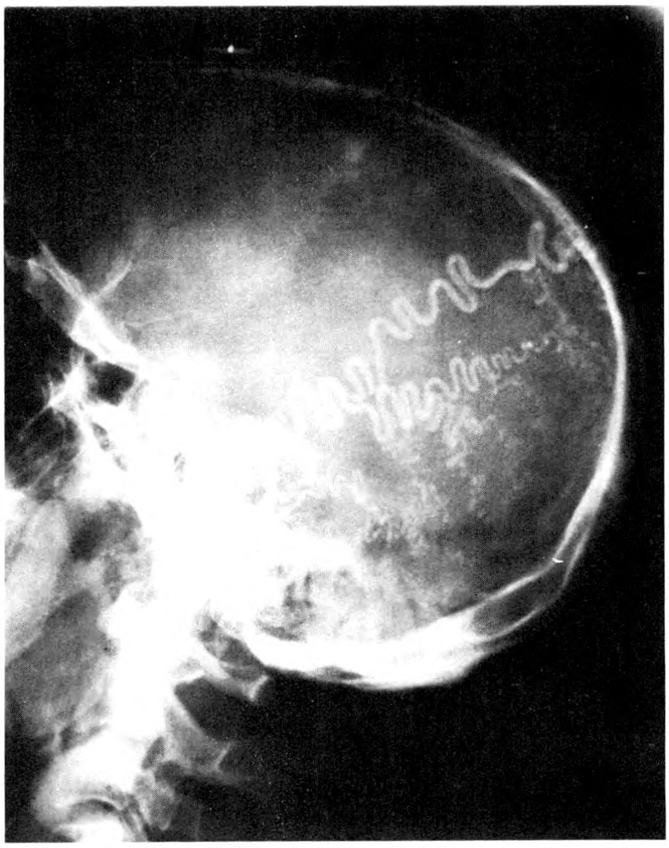

FIG. 2. A later arterial phase of the same angiogram shown in Fig. 1 which demonstrates reformation of the superficial temporal artery in a retrograde fashion by branches of the occipital artery. The greatly dilated external jugular vein shows early opacification.

reported. Tonnis and Lange-Cosack[46] have described an example of familial AVM involving the cerebral vessels.

Incidence

Many authors[1,2,7] believe that AVMs are more common in the scalp than in any other part of the body, and according to Watson and McCarty,[49] over 50% of them occur in the head region. Olivecrona and Ladenheim[28] have reported that scalp AVMs are about 20 times less common than the intracranial AVMs. Of 158 cases of scalp AVMs that were reviewed, in 85 (55%) there was no history of trauma. Of these, 15 patients had either a birthmark at the site of lesion or the lesion was present at birth. Two of these instances occurred in sibs.[19] Of the remaining 73 cases, in 66 (43%) there was a history of non-penetrating or penetrating injury. Three of these patients had port-wine stains which apparently became symptomatic following trauma. Of the remaining seven cases, five were iatrogenic AVMs, due to temporal arteriotomy[6,16,22] and two were possible false aneurysms.[4,40]

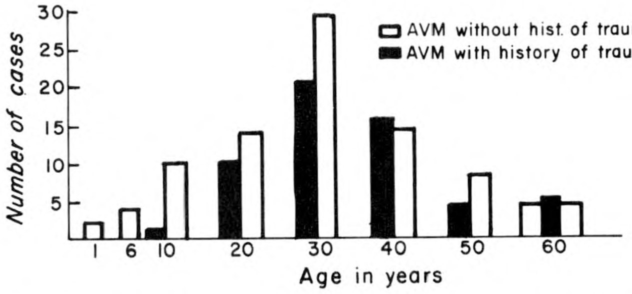

FIG. 3. Age incidence of 143 scalp AVMs. Fifteen patients in whom the age was not recorded are not included.

Some authors consider the congenital AVM to be more common[1,15,47] and others express an opposite view.[17,42] Owing to the difficulties in distinguishing between the true congenital and the traumatic AVMs, relative incidence of these lesions cannot be established with certainty.

Age

The third decade was the period in which the highest incidence was found in both congenital and traumatic forms. The youngest patient of the non-traumatic group was 3 months and the oldest 59 years. In the traumatic group, the youngest one was 8 years and the oldest 61 years (Fig. 3).

Sex

In both groups, the condition was more common in males than in females. Of 84 patients with no history of trauma in whom sex was given, 48 (60%) were male and 36 (40%) were female. Of 68 patients with history of trauma 46 (66%) were male and 22 (34%) were female.

Location

In both groups the AVM occurred almost equally in the frontal, temporal, and occipital scalp (Table 1). The incidence of AVM in these regions was almost two times greater than the posterior auricular and parietal areas. No traumatic AVM was found in the posterior auricular region.

Combined Extracranial-Intracranial AVM

AVMs involving both intracranial and extracranial vasculature[5,9,14,34] are thought to arise from a single embryonic maldevelopment which has failed to be split completely into layers.[14,28] This concept is not in agreement with the principle of development of the head vasculature in the embryo. The brain arteries are derived from the internal carotid arteries (they are later connected with the vertebrobasilar system) during the stage that the embryo is about 30 days old and 5 to 8 mm.[30,31] The scalp arteries are derived from the external carotid arteries in a later stage when the embryo is about 6 weeks old and 18 mm. to 26 mm. Before this stage, the thin

TABLE 1. *Distribution of 148 Scalp AVMs. Five Iatrogenic Malformations and Two Possible False Aneurysms are not Included. In Three Additional Cases the Site of the Lesion was Not Recorded.*

	FRONTAL					PARIETAL				TEMPORAL					OCCIPITAL				POSTERIOR AURICULAR				HALF OF THE SCALP				ENTIRE SCALP	TOTAL
	Right	Left	Bifrontal	Side not given	Total	Right	Left	Biparietal	Total	Right	Left	Bitemporal	Side not given	Total	Right	Left	Bioccipital	Total	Right	Left	Side not given	Total	Right	Left	Side not given	Total		
AVMs without history of trauma	7	5	6	1	19	4	1	2	7	9	6	0	2	17	4	6	9	19	5	1	2	8	4	5	0	9	4	83
AVMs with history of trauma	6	7	5	0	18	3	1	1	5	11	11	1	0	23	2	5	4	11	0	0	0	0	0	3	1	4	4	65
Total					37				12					40				30				8				13	8	148

scalp covering the membranous skull is avascular and is separated from the skull by a considerable interval of avascular tissue.[30] The emissaries later develop and communicate the intra- and extracranial vasculature.

Thus, it seems that there is a separate origin for the scalp, dura, and cerebral congenital AVMs and when a combined extracranial-intercranial AVM occurs it is due to a secondary communication.

Communication of the Scalp AVM with Intracranial Venous Sinuses

No example of this abnormality was found among the reported traumatic AVMs. Congenital arteriovenous communication between the occipital artery and transverse sinus has been reported.[11,27,44,47] We have also observed communications between a scalp AVM and superior sagittal sinus.[19]

In the embryo, the dural sinuses originate from the dural plexus and develop independently from the scalp and the brain vasculature. The superior sagittal sinus is formed by an anterior subdivision of the plexus when the embryo is 6 weeks old. The transverse sinus develops from the tentorial plexus and later joins the superior sagittal sinus.[43]

It appears that the sinus communication of the scalp AVM develops in a later period when the emissary veins are formed, and depending on the location of AVM, the communication takes place either through the persistent primitive vessels or ordinary emissary veins. The size of the skull defect through which the communicating vessels pass is determined by the diameter of these communicating structures.[19]

Association with Other Abnormalities

Multiple intracerebral AVMs and association of intracerebral AVM and congenital aneurysm are occasionally reported.[32,41,45] No such multiplicity or association was noticed in the cases reviewed in the present study. Nevertheless, a patient with congenital venous malformation of the scalp associated with plexiform neurofibroma and cranial defect has been recently described.[24]

Clinical Picture and Treatment

Symptoms and signs of the scalp AVM are well described and they range from a simple disfiguration to a life threatening hemorrhage. Tinnitus and throbbing which are aggravated by physical activities may become most troublesome to the patient. Thrill and bruit are usually present. Papilledema is uncommon and its pathogenesis is not clear. Cardiac symptoms and failure are rare complications of the scalp AVM. An angiogram discloses the nature of the disease. The ideal treatment is complete excision of the AVM as is demonstrated in Case 1 in Group One. Partial excision and ligation of the feeding vessels or carotid artery do not usually bring permanent relief (Case 2, Group One). Other methods of therapy such as x-ray radiation, injection of sclerosing solution, electrocoagulation and compression are rarely successful. It is also doubtful that artificial embolization could be used as a definitive therapy, unless it is combined with total resection.

It is best to identify the feeding arteries from the angiograms and ligate them first before exposing the AVM. A skin flap larger than the main bulk of the lesion is preferable for the ease of dissection and reduction of the bleeding. When possible, the AVM is removed in one piece, piece-meal excision increases the amount of bleeding and the operating time. Whatever surgical technic is used total excision is essential for permanent cure.

Summary

Six illustrative instances of arteriovenous malformations of the scalp, one of which proved fatal are presented. A further 152 cases are analyzed. Of 158 cases, 85 patients (55%) had no history of scalp injury. Of these, two occurred in sibs. Of the remaining 73 cases, 66 patients (43%) had a history of non-penetrating or penetrating scalp trauma, five had iatrogenic AVMs and two were thought to be false aneurysms. Sixty per cent of the instances without history of trauma and 66% of the instances with history of trauma occurred in men. The highest incidence in both groups were seen during the third decade. The common sites for both groups were frontal, temporal, and occipital regions. The parietal and posterior auricular areas were less commonly involved. On the basis of the cerebrovascular embryology, it is stated that there ought to be a separate origin for the scalp, dura, and cerebral congenital AVMs and when a combined extracranial-intracranial AVM occurs it is due to a secondary communication. Finally, it is concluded that the best therapeutic results are obtained by early diagnosis and complete surgical excision.

Acknowledgment

The author wishes to thank Dr. Mark M. Mishkin for permission to report Case 2 of Group One patients and Dr. Herbert I. Goldberg who kindly supplied Figures 1 and 2.

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The Sympathetic Response in Head Trauma; Catecholamine and Cardiopulmonary Changes upon Altering P_{CO_2}

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THE MAJORITY of patients with severe head trauma have increased intracranial pressure, and studies in animals have consistently demonstrated that increasing the intracranial pressure is followed by an increase in the systemic arterial pressure.[1–4,6–9,11,14] Cushing, in 1901, demonstrated that the blood pressure elevation did not occur if the cervical spinal cord was sectioned or if cocain was applied to the medulla.[4] Other investigators have confirmed and extended these studies so that it has become generally accepted that the rise in systemic arterial pressure which accompanies the increase in intracranial pressure is mediated by the sympathetic nervous system. It has also been suggested that the adrenal medullary secretion is increased under these conditions[8] and the pulmonary edema seen in some instances is the result of marked sympathetic action on the heart and peripheral vascular bed.[5]

Despite this evidence of the role played by the sympathetic system in the cardiovascular response to increased intracranial pressure, there have been no reports of the biochemical assay of the neurohormones, epinephrine, and norepinephrine, in patients with head trauma.

In the three patients described in this report, increased intracranial pressure was produced by carbon dioxide breathing under controlled conditions. The systemic and pulmonary vascular changes, as well as epinephrine and norepinephrine excretion, were measured.

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Case Reports

Case I. D.W., a 50-year-old-man, was admitted to the University of Maryland Center for the Study of Trauma in a comatose state. He had a history of chronic alcoholism and had been found unresponsive several hours previously. No specific episode of trauma was known. No other pertinent past history was obtainable.

On physical examination at admission the patient responded to painful stimuli by assuming a decerebrate posture. The pupils were equal and reactive. There was no definite localizing neurologic sign. There was no evidence of recent head or other trauma. The blood pressure was 170/80 mm. Hg; the pulse rate was 8 and regular. Urine obtained after urethral catheterization was normal. Routine hemoglobin, urinalysis, serum electrolytes, BUN and creatinine were in the normal range. SGOT was 50 IU/ml and LDH was 150 IU/ml. An electrocardiogram showed left axis deviation, but there were no other criteria of ventricular hypertrophy. A chest X-ray was essentially normal. Bilateral carotid arteriography revealed a probable intracranial space-occupying lesion on the left.

The patient underwent operation on the day of admission. Through left frontal, temporal, and parietal trephines, a 100-125 cc. chronic subdural hematoma was evacuated. A 9.6 French rubber intraventricular catheter was placed through the frontal trephine and was brought out through the scalp, maintaining its sterility under dressings. The patient was then returned to the Center for the Study of Trauma. An indwelling Teflon cannula was placed in the femoral artery for continuous pressure monitoring and blood sampling. A 5 Fr. balloon-tipped Swan-Ganz catheter was passed into the pulmonary artery where its position was confirmed by a chest roentgenogram and by satisfactory "wedging" of the pressure wave by inflation of the balloon. Another catheter was passed (percutaneously) through the right subclavian vein into the right atrium at its junction with the

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superior vena cava; its position was also confirmed by chest roentgenogram. The patient was maintained on mechanical ventilation using an Engstrom Model 300 ventilator. A tracheostomy was performed using a No. 7 cuffed tube. Intracranial pressure was monitored continuously by means of a pressure transducer attached to the intraventricular catheter.

In the postoperative course the patient had continued decorticate posturing on stimulation with occasional spontaneous decorticate activity on his right side. The intracranial pressure remained at a level of around 15 mm. Hg. The mechanical ventilator was set at a minute ventilation sufficient to maintain the alveolar P_{CO_2} at a level of between 25–30 mm. Hg. as monitored by a mass spectrometer. Beginning immediately after operation, methylprednisolone 60 mg. i.v. was given every 6 hours for 2 days, and then 40 mg. i.m. for 3 more days.

On the third day postoperatively, the intracranial pressure rose spontaneously to 40 mm. Hg; the arterial P_{CO_2} was 30 mm. Hg. The neurological condition deteriorated, and spontaneous movement was lost. It was felt that the neurological lesion was irreversible; accordingly, he was admitted to the protocol of Special Intracranial Pressure Studies, a brief description of which follows:

Complete informed consent to perform the studies was obtained from the responsible family members. The patient was maintained on the Engstrom 300 ventilator at a minute ventilation sufficient to maintain the alveolar P_{CO_2}, as monitored continuously by a mass spectrometer[17], at 25–30 mm. Hg. Mean airway pressure was measured with a Statham pressure transducer. Minute ventilation was measured and recorded using a Fleisch pneumotachometer calibrated for the study. Arterial, right atrial, pulmonary artery, and pulmonary wedge pressures were measured using Statham pressure transducers and recorded on a polygraph. Cardiac output was measured by the dye-dilution method using a 5 mg. dose of Cardiogreen injected as a bolus through the pulmonary artery catheter while simultaneously sampling the femoral arterial blood through a Beckman Cardiodensinometer cuvette. Cardiac output was then calculated from the curve generated. Peripheral resistance was calculated from the simultaneously recorded mean arterial pressure and the right atrial pressure difference, divided by the cardiac output, times 80. Pulmonary vascular resistance was measured from the simultaneously recorded mean pulmonary artery pressure—pulmonary artery wedge pressure difference times 80, divided by the cardiac output. Simultaneous recording was also made of the intracranial pressure. Three cc. blood specimens from femoral and pulmonary artery catheters were drawn anaerobically into heparinized syringes. Blood pH, P_{O_2}, and P_{CO_2} were measured on an Instrumentation Laboratories blood-gas analyzer. O_2 saturation was derived from a nomogram and corrected for pH and P_{CO_2}. Oxygen contents were then calculated by the formula: $C = \text{Hgb Gm.}/100\text{ ml} \times 1.39 \times O_2 \text{ saturation} + .003 \times P_{O_2}$. Alveolar P_{O_2}, corrected for water vapor and atmospheric pressure, was measured directly using the mass spectrometer, and mean pulmonary capillary O_2 content calculated from this value. Intrapulmonary shunt was then calculated from this and the pulmonary and systemic arterial O_2 contents.[17]

The patient was then given a dose of d-tubocurarine sufficient to insure and sustain complete flaccidity (at least 30 mg. i. v.). The level of alveolar P_{CO_2} was gradually raised by adding a mixture of oxygen, nitrogen, and carbon dioxide to the ventilator intake, maintaining alveolar P_{O_2} as measured simultaneously by the mass spectrometer constant at about 350 mm. Hg. The intracranial pressure was also continuously monitored. After a period of 50 minutes, while the alveolar P_{CO_2} was held at 55 mm. Hg, another complete set of pressure measurements and a cardiac output were obtained. Urine specimens were collected at 10-minute intervals; these were assayed for epinephrine and norepinephrine. Immediately at the conclusion of these measurements, the exogenous carbon dioxide was withdrawn from the ventilator intake, and the alveolar P_{CO_2} was monitored until it reached the previous baseline level. This required about 5 minutes, and another 25 minutes was alloted to permit stabilization. Alveolar P_{O_2} was held constant. At this point, a repeat of all of the measurements was done.

Case 2. R. H. was a 35-year-old man who was riding in the right front seat of an automobile when it hit a truck; he sustained a severe head injury and was taken to another hospital. He had lacerations about the forehead and was in a deep comatose state. He was transferred to the Center for the Study of Trauma, and on arrival, he was comatose, had multiple bruises and abrasions of the forehead, a compound comminuted fracture over the right supraorbital rim, and multiple lacerations over the right eyelid. The left pupil was partly constricted and minimally reactive to light; the right pupil was dilated and fixed. The blood pressure was 120/80 mm Hg and pulse 100 per minute. The chest was clear to auscultation and percussion, and the heart had a normal sinus rhythm. The patient had spontaneous decerebrate seizure activity, increased muscular tone, and bilateral Babinski reflexes. He reacted to deep pain by decerebrate posturing. The patient was taken to the operating room, where a right frontal craniotomy was done with debridement of a right frontal depressed fracture and suture of lacerated dura. A catheter was inserted into the ventricle, and the multiple lacerations were sutured.

A tracheostomy was made for management of respiratory secretion, and the patient was put on an Engstrom respirator. A chest x-ray was essentially normal. The intraventricular pressure was 16 mm. Hg. A Swan-Ganz catheter was passed into the left pulmonary artery, and another catheter was inserted percutaneously through the right subclavian vein into the right atrium.

A study of the effect of increasing the concentration of C_{O_2} in the inspired air was done in a similar fashion as that described for patient D. W. above, on the first, third, and fifth days postoperatively.

Case 3. R. M., a 41-year-old man, sustained a fracture-dislocation of the seventh cervical vertebra, with paraplegia below the level of C-7. There was no head injury, and the neurologic examination was negative except for the paraplegia. There was no chest or other injury. A Queckenstedt test done at the time of lumbar puncture indicated a complete spinal canal block, most probably at the level of cervical injury. A tracheostomy was made on admission for management of the airway. A chest x-ray was unremarkable. The cervical fracture was reduced by closed methods and head tongs were placed. Eighteen days following injury, when his condition was well stabilized but at a time when he still had a tracheostomy, this patient's response to inhalation of CO_2 was studied in the manner described above, including curarization. Informed consent had been obtained from the patient himself. A Swan-Ganz catheter was passed into the left pulmonary artery, and catheters placed in the right femoral artery and right atrium. No intracranial catheter was placed.

Results

The results of the studies performed in Case 1, D. W., are presented graphically in Figures 1, 2, 3 and in Table

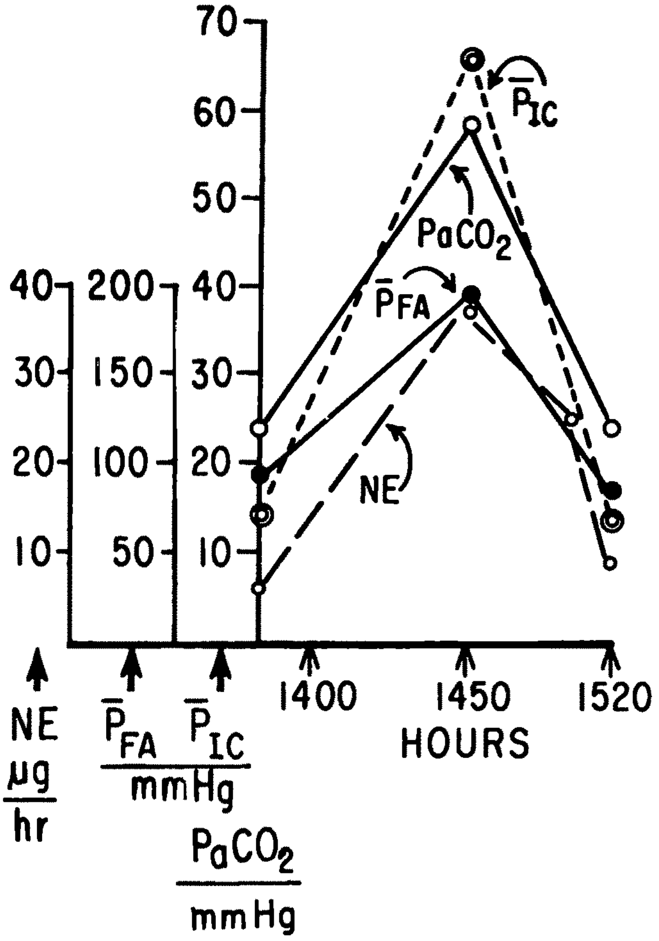

FIG. 1. Case 1, D. W., A patient with irreversible head trauma. The response of femoral artery pressure ($\bar{P}_{FA}$), intracranial pressure ($\bar{P}_{IC}$), and norepinepherine (NE) excretion to alteration of arterial Pco$_2$) (Paco$_2$) are shown.

I. Intracranial pressure initially was 16 mm. Hg and rose to 66 mm. Hg at the peak of arterial Pco$_2$, then returned to 16 mm. Hg on return to baseline Pco$_2$. Most variables returned to baseline values on restoration of baseline Pco$_2$. Cardiac output changed insignificantly on institution of elevation of alveolar Pco$_2$ rising but 0.1 l./min. (6.6 to 6.7 l./min.) and then falling to 5.5 l./min. on return to baseline. However, mean arterial blood pressure rose from 95 to 195 mm. Hg and then returned to 82 mm. Hg. Simultaneously measured systemic vascular resistance rose from 1112 to 2245 and then fell back to 1147 dynes cm. sec^{-5}. Arterial Pco$_2$ correlated closely with alveolar Pco$_2$ being 24, 59, then 25 mm. Hg for the arterial values, compared with 23, 62, 23 respectively, for the alveolar values. Pulmonary arterial pressure rose precipitously from 14 mm. Hg at baseline to 42 and then returned to 14 on restoration of normal alveolar Pco$_2$. Simultaneous pulmonary artery wedge pressure, measured by the Swan-Ganz technic, rose from a baseline of 6.5 to 32 mm. Hg, returning to 8 mm. Hg on restoration of normal Pco$_2$. Calculated total pulmonary vascular resistance changed insignificantly during the study. The excretion rate of urinary norepinephrine rose from 6 µg./hr. to 66.6 µg./hr. at the peak of arterial Pco$_2$ and fell to 25.1 µg./hr. 20 minutes after the restoration of arterial Pco$_2$ to normal, and to 9.6 µg./hr. at 30 minutes. Calculated intrapulmonary shunt, not shown, was 0.16 at baseline, 0.18 at peak Pco$_2$, and 0.17 on return to baseline.

The results of the three studies on patient R. H. are presented in Table 1. During each experiment on this patient, the increase in Pco$_2$ was accompanied by an increase in the intracranial pressure. The increase in the intracranial pressure was seen to be greater at Paco$_2$ concentrations above 30 mm. Hg than at concentrations below this level. As the concentration of the CO$_2$ in the inspired air was decreased, the fall in the intracranial pressure was more rapid than the decrease in the Paco$_2$. The cardiac output increased during the increase of the concentration of Pco$_2$ in the inspired gases in each study, and there was a slight decrease rather than an increase in the peripheral resistance on each occasion. Pulmonary arterial and pulmonary wedge pressures increased also with the administration of CO$_2$, but the pulmonary resistance showed a slight decrease.

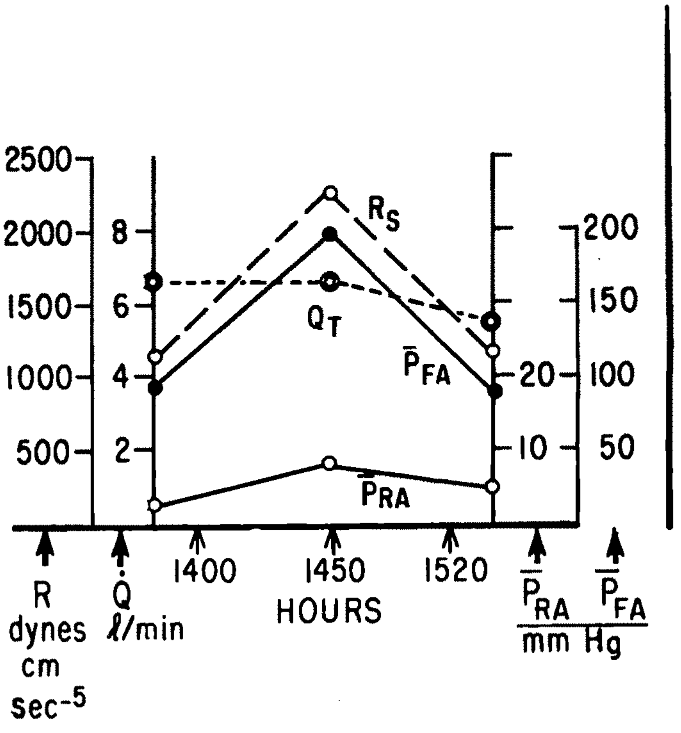

FIG. 2. The same study as in Figure 1, showing the simultaneous effect on total cardiac output (QT), right atrial pressure ($\bar{P}_{RA}$) and systemic vascular resistance (Rs).

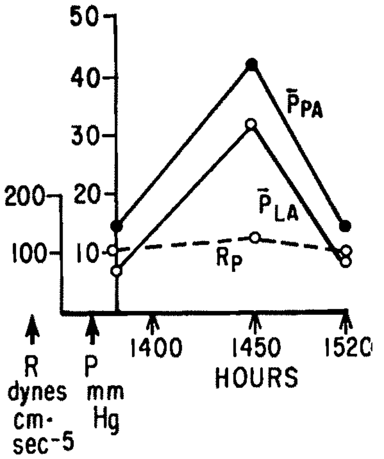

FIG. 3. The same study as in Figures 1 and 2, showing the effect on pulmonary artery ($\bar{P}_{PA}$) and pulmonary artery "wedge" ($\bar{P}_{LA}$) pressures and pulmonary vascular resistance.

The excretion rates of epinephrine and norepinephrine were observed to rise in both Case 1 and Case 2 following the increase in intracranial pressure. In the second experiment on patient R. H., it was observed that the increase in urinary excretion of norepinephrine rose promptly following the increase in the intracranial pressure; and in the first and third experiments on patient R. H., the norepinephrine was found to increase to a considerable extent, but the rate of response was somewhat slower; however, the rate of response may have been related to the volume of urine being excreted by this patient, because the urine excretion rates in ml./min. were considerably less for patient R. H. than for patient D. W.

In Case 3, the patient with transection of the cervical cord showed the findings presented in Table 2. Despite the fact that the arterial P_{CO_2} more than doubled from 20 mm. Hg to 46 mm. Hg, there was no change in the pulmonary pressures nor in the mean arterial pressure or heart rate. The value for the cardiac output rose from 6.53 to 7.46, and the calculated peripheral resistance decreased approximately 13%. Rather than an increase in the norepinephrine excretion rate as was observed for the patients with head injury, this patient had a decrease from 0.71 to 0.14 μg./hr.

Discussion

In 1901, Cushing pointed out that "an increase of intracranial tension occasions a rise of blood pressure which tends to find a level slightly above that of the pressure exerted on the medulla".[4] His studies included investigation of the effects of localized pressure on various areas of the brain, effects of section of the spinal cord, and the effect of cocain on the medulla. Since the latter two procedures abolished the increase of systemic blood pressure due to increased intracranial pressure, Cushing concluded that the increase in the systemic blood pressure arose from pressor sensitive areas in the medulla and was mediated by the sympathetic nerves. The involvement of the sympathetic nervous system has been confirmed by numerous physiological and pharmacological investigations.[1–3,6–9,14] However, we have not found biochemical assays of the norepinephrine or epinephrine in the blood or urine of animals or humans in which the effects of increased intracranial pressure have been investigated; this is probably due to the lack of sensitivity of the previously available technics.

TABLE 1. *Intracranial Pressure, Cardiovascular and Pulmonary Parameters in Patients with Severe Head Trauma*

Spec. No.	Time	NE Ex. Rt.	ICP	Heart Rate	Pcv	Part	Ppa	Pw	C.O.	PA_{CO_2}	PA_{O_2}	Pa_{CO_2}	Pa_{O_2}	pH	Rsys	Rpul	QS/QT
	Patient D. W.																
1	1400	6.02	16.0	100	3.5	95	14	6	5.1	22	450	24	181	7.31	1112	91	.23
2	1450	66.56	66.0	117	7.0	195	42	32	5.0	62	375	59	163	7.21	2245	119	.26
3	1520	9.65	16.0	105	4.0	82	14	8	4.2	23	497	25	189	7.48	1147	88	.23
	Patient R. H.																
Study I																	
1	1715	4.97	13.5	110	1.0	115	12	4	5.4	12	332	14	149	7.64	1704	118	.17
2	1745	4.34	37.6	100	4.0	200	31	23	10.0	41	300	37	189	7.61	1584	64	.18
3	1810	9.71	11.0	125	0.0	125	13	7	4.9	14	330	20	199	7.43	2053	99	.09
Study II																	
1	1130	3.11	6.5	90	5.0	108	12	5	5.7	21	350	39	164	7.46	1443	105	.21
2	1200	12.22	24.0	99	5.0	136	16	7	9.3	28	421	42	173	7.42	1123	80	.30
3	1210	8.35	46.8	90	5.0	155	23	14	—	38	375	53	153	7.35	—	—	—
4	2133	11.10	36.7	100	7.1	140	17	7	—	34	320	47	147	7.34	—	—	—
5	1250	11.34	12.4	110	5.0	110	12	3	7.0	23	325	38	148	7.40	1193	93	.22
Study III																	
1	1035	1.87	8.0	80	6.5	112	19	16	4.8	16	300	21	127	7.64	1772	50	.16
2	1050	1.50	12.0	50	7.5	125	18	14	—	25	300	33	171	7.50	—	—	.14
3	1123	1.61	33.5	60	12.0	145	28	23	6.1	35	300	42	200	7.40	1734	64	.11
4	1153	6.35	41.1	78	14.5	162	34	27	7.8	44	300	48	183	7.34	1522	69	.15
5	1210	7.83	8.0	85	8.0	125	22	16	6.7	33	300	40	166	7.42	1394	80	.17
6	1227	8.80	2.0	70	4.0	105	15	10	6.7	23	300	35	161	7.47	1204	52	.14

In the patients with severe head trauma, evaluation of the effectiveness of treatment during the acute stage of the injury requires information on the intracranial pressure (ICP), and the placement of an intraventricular catheter has been found to be the best method of obtaining accurate measurements of the ICP.[10] We have utilized the opportunity to investigate the relationships between intracranial pressure, systemic blood pressure, and pulmonary cardiovascular parameters in these patients with the aim of establishing the basis for evaluating present methods of therapy and developing improvements in therapy.

Of all agents known to act on the cerebral vessels, CO_2 has the most potent effect on the cerebral blood flow, as has been pointed out by Sokoloff in his review of the effects of CO_2 on cerebral circulation.[16] Paul, *et al.*[12] from this Center have described the relationships between arterial Pco_2 and intracranial pressure in patients studied who have had injuries of sufficient severity to require the use of a respirator, and where it has also been possible to administer tubo-curarine during the period of study to avoid artifacts and involuntary respiratory movement due to the elevation of arterial $Paco_2$.

In the patients with severe head trauma who are reported in this paper, there is evidence for increased sympathetic nervous activity with increases in the ICP produced by elevating the arterial Pco_2. However, direct effects of CO_2 on the cardiovascular system, on the sympathetic nerves, and on the adrenal medulla must be considered. Effects of CO_2 on the cardiovascular system have been reviewed by Price.[13] The studies in man are few and often poorly controlled. In animals, the studies of CO_2 effects have been complicated by "basal" anesthetics, surgical stimulation, and inadequate control of variables. In the studies on both men and animals, the achievement of a steady state during CO_2 inhalation was rare. Of the cardiovascular actions exerted by CO_2 in man, the effect on the heart is to decrease the force of contraction and the rate. This effect may be due to the effect of CO_2 on lowering the pH of the blood rather than to the CO_2 itself. Elevation of the arterial Pco_2 has been shown to decrease the resistance of most vascular beds and to increase their blood flow. It would be difficult to interpret the direct peripheral vascular effects of CO_2 inhalation in nonanesthetized individuals in whom psychic stress induced by a heightened respiratory drive is active.

Thus, the direct effects of CO_2 on the heart and blood vessels have been shown to be depression as opposed to the stimulation which was observed in our head trauma patients. Sechzer *et al.*, have described elevations of the blood catecholamines in human subjects after inhalation of carbon dioxide;[15] the results of their studies indicated there was an increase in sympathetic nervous activity, but the blood catecholamine levels were studied in only a few of their patients (in seven of 27 studied), and only two specimens of each subject were examined, one before and one during inhalation of CO_2. In addition, these investigators were not able to attain steady state conditions because their subjects were conscious and voluntary movements were not blocked.

In the studies reported here, we have examined the urinary excretion of epinephrine and norepinephrine in serial urine specimens before, during, and after the inhalation of CO_2. The levels of these catecholamines in the urine reflects endogenous formation and release. Urine measurements permit serial study without interference with hemodynamics; frequent blood assays of these hormones would require withdrawals of inordinately large blood samples. Using the assay of serial urine specimens, we have found that a rise in the systemic arterial pressure is followed by an increase in the rate of urinary excretion of norepinephrine, and usually a lesser increase in epinephrine.[5]

The serial collection of urine specimens during periods of increase in intracranial pressure permits us to differentiate between the relative contributions of the sympathetic nervous system and the adrenal medulla, as reflected in the urinary excretion of norepinephrine and epinephrine. In the second study on patient R. H., the urinary norepinephrine rose markedly whereas the epinephrine remained much closer to normal levels suggesting a lack of significant release of neurohormones from the adrenal medulla.

Patient R. M., with transection of the cervical cord, provided the opportunity to study the peripheral effects of elevation of arterial carbon dioxide. In this patient, the Cushing reflex was blocked at the level of the transection of the cervical cord fracture; the direct effects of carbon dioxide on the heart, peripheral sympathetic nerves, and adrenal medulla could be evaluated. The lack of change of systemic blood pressure, of heart rate, and the failure to increase the norepinephrine excretion rate, as well as an essentially unchanged epinephrine excretion rate, all indicate that under the conditions of these studies, the direct peripheral effect of carbon dioxide did not produce the changes which are seen in the patients with severe head injury.

Further, more definitive studies on the rate of excretion of norepinephrine and of epinephrine in the patients with severe head trauma are indicated to rule out the possibility of abnormal metabolic pathways. However, as a working hypothesis, it appears that the studies of urinary excretion of norepinephrine and epinephrine have corroborated the conclusions of previous investigators

TABLE 2. *Norepinephrine Excretion Rate, Cardiovascular and Pulmonary Parameters in Case 3, a Patient with Cervical Cord Transection*

Spec. No.	Time Hrs.	NE Ex. Rt. ug/hr	Heart Rate beats/min	Pcv mmHg	Part mmHg	Ppa mmHg	Pw mmHg	C.O.	PA_{CO_2}	PA_{O_2}	Pa_{CO_2}	Pa_{O_2}	pH	Rsys	Rpul	QS/QT
1	1602	0.71	60	6	90	18.5	11.0	6.53	20	345	28	65	7.63	1028	92	.38
2	1630	0.14	60	7	90	23	9.5	6.53	46	345	40	154	7.46	890	145	.30
3	1655	0.37	60	6	85	19	9.0	6.53	22	345	29	84	7.60	1005	127	.35

that there is a marked activation of the sympathetic nervous system when the intracranial pressure rises above about 16 mm. Hg, and more quantitative studies are planned to relate the urinary excretion rate of these catecholamines to their rate of entry into the blood stream.

The marked change in pulmonary artery pressure and pulmonary arterial wedge pressure, during the rise in systemic arterial pressure of patient D. W., is particularly interesting in regard to the mechanism of pulmonary edema in acute head injury, which has been ascribed in animal studies to acute left ventricular failure in response to acute rises in intracranial pressure and systemic arterial pressure.[5] If pulmonary artery wedge pressure may be assumed to reflect left atrial, and thus left ventricular end-diastolic pressures, then evidence in support of this conclusion was obtained in our studies reported here. The intrapulmonary shunt fraction did not change during the period of raised $Paco_2$ in these studies and arterial oxygen content was unchanged as well, excluding myocardial hypoxia as the etiology in these instances. It may be suggested that the catecholamine release documented in the cases reported here produced a marked ionotropic cardiac effect reducing ventricular compliance and hence raising end-diastolic and the pulmonary arterial pressures.[12] The lack of significant epinephrine secretion in these instance implies much or most of this inotropic affect is the result of release of norepinephrine within the myocardium in the cardiac sympathetic nerves rather than blood-borne from the adrenal medulla. An intrathoracic shift in blood volume, associated with marked peripheral vasoconstriction, might also be operative. Which of these factors plays the dominant role cannot be evaluated without further investigation.

The documentation of increased levels of sympathetic neurohormones rationalizes the use of sympathetic blocking agents in those instances in which undue sympathetic activity is found with head trauma.

Conclusions

In patients with severe head trauma, an increase in intracranial pressure (ICP) was produced by an artificial rise in arterial Pco_2, and the increase in ICP was associated with an increase in systemic arterial pressure, pulmonary artery and pulmonary artery wedge pressures, and a rise in urinary catecholamine excretion. These effects were absent in a patient studied with spinal cord transection. The evidence in these cases suggests that, in patients with an intact spinal cord, elevations in ICP produced by elevation of Pco_2 initiate a pressor response which is mediated by the sympathetic nervous system.

Symbols used in Table and Text

NE	—norepinephrine
ICP	—intracrainal pressure
Pco_2	—partial pressure of carbon dioxide
Po_2	—partial pressure of oxygen
P	—pressure
$\bar{P}$	—mean pressure
QT or C.O.	—cardiac output
R	—resistance
Qs/Qt	—intrapulmonary shunt fraction
Suffix	
RA	—right atrium
cv	—central venous
art	—systemic arterial
pa	—pulmonary arterial
W	—"wedge"
A	—alveolar
a	—arterial
sys	—systemic
pul	—pulmonary

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eoperative Localization of Hyperfunctioning Parathyroid Tissue:

Radioimmunoassay of Parathyroid Hormone in Plasma from Selectively Catheterized Thyroid Veins

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THE DIAGNOSIS of primary hyperparathyroidism is usually made with ease, since almost all patients have elevated serum calcium levels and other characteristic biochemical, radiologic and/or clinical findings which allow differentiation from the various disorders associated with hypercalcemia. Occasionally, however, the diagnosis is difficult, and after extensive evaluation the uncertain physician must decide either to manage his patient conservatively or subject him to neck exploration in search of neoplastic parathyroid tissue. The anatomic variability of the parathyroid glands is appreciable and all too commonly more than one neck operation is necessary before the offending lesion(s) is found and removed. Each unsuccessful exploration increases the difficulty, length and morbidity of the subsequent operative procedure.

The development in 1963[2] of a radioimmunoassay for parathyroid hormone (PTH) which allowed direct measurement of this polypeptide in peripheral blood has become a powerful diagnostic tool. Recently Berson and Yalow[1] reported that 53/56 hyperparathyroid patients had higher peripheral plasma PTH levels than 98% of normal controls. Egdahl, Reiss and Canterbury[4] stressed the diagnostic usefulness of the PTH radioimmunoassay and demonstrated that the elevated serum PTH in hyperparathyroid patients dropped to normal following curative surgery.

Over the past few years several methods of localizing neoplastic parathyroid glands preoperatively have been investigated. Arteriography,[6] venography[17] and radioactive selenomethionine scans[9] have been of variable help in localizing large lesions, but the more common small tumors have usually escaped detection. Reiss and Canterbury[13] demonstrated another technic in which measurement of serum PTH was helpful in localizing hyperactive parathyroid tissue. They observed that single parathyroid adenomas could be lateralized by demonstrating elevated peripheral PTH levels following massage of the affected but not the unaffected side of the neck. Patients with bilateral parathyroid hyperplasia showed elevated PTH levels following massage of each side. Others have not found this test as reliable and it probably is of little value in localizing retrosternal or retroclavicular neoplasms. Reitz *et al.*[14] reported the localization of parathyroid adenomas in six patients by measuring PTH in plasma from selectively catheterized large veins in the neck and thorax. With continued use these investigators have found this technic helpful

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in lateralizing lesions in only 50–60% of cases.[10] O'Riordan,[8] however, recently reported the preoperative localization of 70% of neoplastic parathyroids by utilizing this large vein sampling method.

Doppman and Hammond[3] proposed that hyperfunctioning parathyroid glands could best be localized by measuring PTH in plasma from directly catheterized thyroid veins. This hypothesis was based on their observation that venous drainage from both the superior and inferior parathyroid glands was almost always ipsilateral by way of the inferior thyroid vein. Rarely were the middle and superior thyroid veins the main route of drainage. This hypothesis has since been confirmed.[11]

Since 1968 twenty patients at the National Institutes of Health with primary hyperparathyroidism have had PTH radioimmunoassay of plasma samples obtained by Doppman's technic of selectively catheterizing the thyroid veins and the large neck veins. Subsequent neck exploration confirmed the predicted location of hyperactive tissue in each case.

Subjects and Methods

Patients: All patients were admitted to the Clinical Center of the National Institutes of Health. A diagnosis of primary hyperparathyroidism was made in each case on biochemical, radiological, and clinical criteria. The subjects of the study, their age, gender, signs and symptoms leading to diagnosis, and biochemical findings are listed in Table 1.

Catheterization Procedure: Under local anesthesia the Muller guided catheter system (United States Catheter and Instrument Corporation, Glens Falls, New York) was introduced percutaneously into the right femoral vein. The catheter was directed by a 100 cm. guide wire attached to an external handle which deflects and rotates the catheter tip. The procedure was monitored by image intensified fluoroscopic control. Selective samples were obtained from the large veins of the neck and thorax, from the thyroid veins and from the inferior vena cava and its tributaries. The details of this technic have been described elsewhere.[11,17] In patients who had previously had thyroid or parathyroid surgery, inferior thyroid arteriography was first performed so that the thyroid venous plexus could be evaluated and more easily sampled at the subsequent venous catheterization.

Radioimmunoassay: PTH was measured by radioimmunoassay as previously described,[2,16] using ^{125}I-labeled bovine PTH purified by adsorption to micro-fine silica (QuSo)[15] and/or by gel filtration, an antibovine guineapig antiserum GP-1, and a partially purified preparation of human parathyroid hormone as standard.[7] Separation of antibody-bound from free hormone was accomplished by a modification of the dextran-charcoal method of Herbert.[5] The values for PTH in normal fasting subjects range from 0.3–0.8 nanograms (ng) human PTH/ml. plasma.[10] Each sample was assayed six times at a single dilution; from each patient, all samples were measured in the same assay. In all cases, the radioimmunoassay data were available prior to surgical exploration of the neck.

Surgical Technic: All operations were performed by the Surgery Branch of the National Cancer Institute. A standard transverse cervical incision was used in all patients and each side of the neck was explored, a diligent search being made for all four parathyroid glands regardless of the pathology uncovered. In no patient was sternal division and deep mediastinal exploration necessary.

Results

Table 2 shows the PTH radioimmunoassay data from selective venous catheterization samples and the location and histology of the removed parathyroid tissue. All but one patient had more than one of the six thyroid veins catheterized and in 18/20 patients, thyroid venous samples were obtained from both the right and the left side of the neck but not always from the same veins on each side. In 9/20 patients both inferior thyroid veins were successfully catheterized.

Generally, the highest hormone levels were found in the inferior thyroid veins; however, slightly higher levels were found in the ipsilateral innominate vein at its junction with the inferior thyroid vein in two cases (R.B. and W.B.) and in the ipsilateral middle thyroid vein in one case (J.L.).

The mean background level (MBL) of PTH represents the average of the PTH levels in 5 plasma samples taken from separate peripheral veins below the diaphragm. As seen in Table 2, this was above normal (greater than 0.8 ng/ml.) in all but four patients.

By comparing the MBL with the PTH levels in the thyroid veins one could accurately predict which side of the neck contained hyperfunctioning parathyroid tissue. In each of the 20 cases it was observed that neck vein PTH values more than twice MBL were indicative of ipsilateral hyperfunctioning parathyroid tissue. Plasma PTH gradients were unilateral and usually higher in those patients with single adenomas than in patients with bilateral parathyroid hyperplasia who, in all but one case (H.D.), had bilateral PTH elevations. In patient H.D. the previously ligated right inferior thyroid vein could not be catheterized and there was a PTH elevation less than twice the MBL in the right middle thyroid vein even though a right inferior hyperplastic gland was present. This is the only instance where a lesion was found but not predicted by the PTH radioimmunoassay and emphasizes the importance of obtaining venous samples from the inferior thyroid veins when possible.

TABLE 1

Patient	Age	Gender	Presenting Signs & Symptoms	Ca (mgm%)	PO_4 (mgm%)	Alk. Phos. (I.U.)
A.A.	45	F	Duodenal ulcer, pancreatitis, nephrolithiasis; previous neck exploration for hyperparathyroidism	12.0	3.5	15*
R.B.	62	M	Persistent hypercalcemia following previous neck exploration for hyperparathyroidism	11.2	2.0	56
W.B.	39	M	Nephrolithiasis	12.0	2.2	66
H.I.	62	F	Nephrolithiasis	11.7	1.2	122
P.J.	53	F	Hypercalcemia found incidentally	12.0	2.3	128
J.J.	50	F	Perforated pyloric ulcer	11.0	1.9	79
O.J.	48	F	Gastric ulcer	13.5	1.9	98
V.R.	50	F	Gastric ulcer	12.0	2.7	65
Ed.Wo.	59	F	Acute psychosis with depressive reaction	11.9	1.8	80
M.S.	60	M	Nephrolithiasis, gastric ulcer; previous neck exploration for hyperparathyroidism	11.6	2.4	68
E.H.	50	M	Nephrolithiasis	10.7	3.0	65
C.D.	66	M	Hypercalcemia found incidentally	13.5	2.2	90
S.B.	52	M	Persistent hypercalcemia following removal of two normal parathyroid glands	17.0	1.7	150
O.V.	40	F	Severe bone pain; neoplastic parathyroid glands previously resected	14.9	1.8	123
E.W.	39	M	Nephrolithiasis; neoplastic parathyroid glands previously resected; previous total thyroidectomy	11.3	2.8	74
G.D.	47	M	Asymptomatic member of hyperparathyroid kindred	12.8	2.7	75
H.D.	43	M	Microscopic hematuria; hyperplastic parathyroid gland(s) previously resected	11.2	1.7	41
J.H.	61	F	Asymptomatic member of hyperparathyroid kindred: previous thyroidectomy	11.6	2.8	53
J.L.	50	F	Asymptomatic member of hyperparathyroid kindred	11.6	2.1	37
J.P.	21	F	Asymptomatic member of hyperparathyroid kindred	11.5	3.2	62

* King Armstrong Units

We were unable to predict the specific parathyroid gland involved and even in retrospect we did not find superior or inferior gland lesions associated with any particular pattern of PTH elevation.

The PTH values of the selective venous samples in four patients are shown in Figures 1a, 1b, 2a, and 2b. In patient E.W. (Fig. 1a) and patient P.J. (Fig. 1b) PTH levels more than twice MBL were present in the left inferior thyroid vein. In each patient a single adenoma involving the left inferior parathyroid gland was found. In patient J.L. (Fig. 2a) and patient J.H. (Fig. 2b) PTH levels exceeding twice MBL were present bilaterally, and both patients had bilateral parathyroid hyperplasia.

If one had evaluated only the PTH levels in the innominate and jugular veins, localization would have been possible in less than half of the cases.

There were eight patients in this series who had previously had neck explorations for either hyperparathyroidism or thyroid carcinoma. In each of these, neoplastic parathyroid tissue was localized as predicted by the venous sampling. In two patients, S.B. and E.W., however, the serum calcium fell transiently postoperatively, but is currently above normal. In patient S.B. both sides of the neck were explored and an 8 Gm. adenoma was found on the right. Patient E.W. also had neoplastic parathyroid tissue located as predicted by the PTH radioimmunoassay and both neck and anterior mediastinum were extensively explored through the cervical incision. Both of these patients are presently being reevaluated.

It is extremely important that the surgeon and the radiologist review the venograms before operation to compare the specific venous sampling sites with the PTH radioimmunoassay values. For example, patient

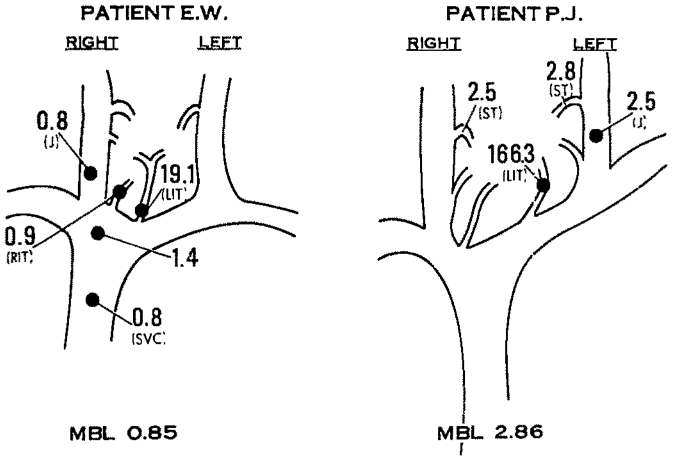

FIG. 1. Plasma PTH concentrations from selectively catheterized veins in two patients; E.W. (1a) and J.P. (1b) with single left inferior parathyroid adenomas. Veins are jugular (J), innominate (I), superior vena cava (SVC), right inferior thyroid (RIT), left inferior thyroid (LIT), superior thyroid (ST). MBL represents the mean background level of PTH (see text). Values of PTH are in ng/ml.

TABLE 2. *PTH Levels Obtained by Selective Venous Sampling (Values in Nanograms/Ml.)*

Patient	MBL (ng/ml.)	Veins Where PTH Level Was Greater Than Twice MBL	Level of PTH In Sampled Vein (ng/ml.)	Location of Lesion	Histology of Lesion
A.A.	1.2	R.S.T.	3.2	Rt. Sup.	Adenoma
R.B.	0.8	L.I.T.	19.4	Lt. Sup	Adenoma
		L.Inn.	20.1		
W.B.	1.0	L.I.T.	6.9	Lt. Sup.	Adenoma
		L.Inn.	8.3		
H.I.	1.6	R.M.T.	16.6	Rt.Inf.	Adenoma
P.J.	2.9	L.I.T.	166.3	Lt. Inf.	Adenoma
J.J.	1.8	R.I.T.	29.2	Rt. Sup.	Adenoma
		R.S.T.	5.0		
O.J.	0.8	R.S.T.	2.2	Rt. Inf.	Adenoma
		R.Jug.	5.8		
V.R.	1.5	R.I.T.	33.3	Rt. Inf.	Adenoma
		R.Inn.	3.3		
Ed.Wo.	0.9	L.I.T.	19.1	Lt. Sup.	Adenoma
M.S.	2.1	L.I.T.	33.0	Lt. Inf.	Adenoma
		R.I.T.	33.0*		
		L.M.T.	8.8		
E.H.	1.2	R.I.T.	14.0	Rt. Inf.	Adenoma
C.D.	1.9	L.I.T.	22.6	Lt. Inf.	Adenoma
S.B.	3.4	R.I.T.	22.9	Rt. Inf.	Adenoma
O.V.	7.1	R.I.T.	300.0	Rt. Inf.	Adenoma
		R.Inn.	33.3		
E.W.	1.4	L.I.T.	25.0	Lt. Inf.	Adenoma
		L.M.T.	4.6		
G.D.	0.9	R.M.T.	3.9	All 4 glds.	Hyperplasia
		L.S.T.	2.3		
H.D.	0.7	L.I.T.	2.3	Lt. Sup.	Hyperplasia
				Lt. Inf.	
				Rt. Inf.	
J.H.	0.7	L.I.T.	9.8	Lt. Inf.	Hyperplasia
		R.I.T.	1.6	Rt. Inf.	
		L.Inn.	1.9		
J.L.	1.3	L.I.T.	21.0	Rt. Sup.	Hyperplasia
		R.I.T.	7.3	Rt. Inf.	
		R.M.T.	10.5	Lt. Inf.	
J. P.	0.9	L.M.T.	3.2	Lt. Inf.	Hyperplasia
		R.S.T.	2.0	Rt. Inf.	
		L.Inn.	3.4		

* Right Inferior thyroid vein ligated at previous surgery, only blind vein remnant present (Fig. 3).

MBL = Mean Background Level of PTH
LIT = Left Inferior Thyroid Vein
RIT = Right Inferior Thyroid Vein
LMT = Left Middle Thyroid Vein
RMT = Right Middle Thyroid Vein
LST = Left Superior Thyroid Vein
RST = Right Superior Thyroid Vein
L.Inn. = Left Innominate Vein
R.Inn. = Right Innominate Vein
L.Jug. = Left Jugular Vein
R.Jug. = Right Jugular Vein

M.S. (Fig. 3) during a previous neck exploration for hyperparathyroidism had a normal right inferior parathyroid gland removed and the right inferior thyroid artery and vein ligated. Subsequently, at venous catheterization both the left inferior thyroid vein and the right inferior thyroid vein remnant were catheterized and PTH values of 33 ng/ml. were present in both. Ordinarily this would suggest bilateral lesions and while this could not be definitely excluded, it was thought that the sample from the ligated right inferior vein sample represented blood which had refluxed from the left inferior or common thyroid vein. At operation a left inferior parathyroid adenoma was removed from the superior mediastinum. Only a normal superior parathyroid gland was present on the right side. Postoperatively the serum calcium returned to normal and the patient made an uneventful recovery.

The direct relationship between the serum calcium level and parathyroid tumor size has long been appreciated. To determine if the preoperative serum calcium, the MBL and the tumor volume varied directly with one another correlation coefficients were calculated between these parameters. The tumor volume (in cm^3) was calculated from the formula for the volume of a spheroid, $V = \frac{4}{3}\pi abc$ where a, b and c are the lengths of the major axes. In cases of hyperplasia the volumes of the involved glands were added together. There was a significant positive correlation between preoperative serum calcium and MBL ($r = 0.62$, $p < 0.005$), tumor volume and preoperative serum cal-

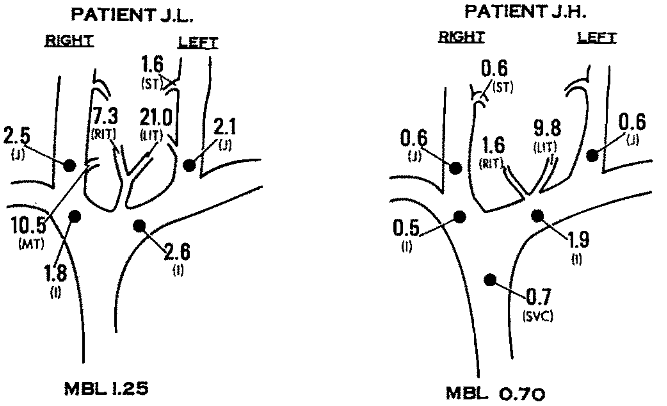

FIG. 2. Plasma PTH concentrations from selectively catheterized veins in patients J.L. (2a) and J.H. (2b) with bilateral parathyroid hyperplasia. Note that in each patient PTH levels twice that of MBL are present in both the right and left inferior thyroid veins. Veins are jugular (J), innominate (I), superior vena cava (SVC), right inferior thyroid (RIT), left inferior thyroid (LIT), superior thyroid (ST), and middle thyroid (MT). MBL represents the mean background level of PTH (see text). Values of PTH are in ng/ml.

TABLE 3

Parameters	r	p
MBL and tumor volume	0.83	<0.001
MBL and preoperative serum calcium	0.62	<0.005
Tumor volume and preoperative serum calcium	0.80	<0.001

This table depicts correlation coefficients between MBL and preoperative serum calcium, MBL and tumor volume, and tumor volume and preoperative serum calcium in 19 patients with primary hyperparathyroidism. MBL represents mean background level of PTH (see text).

cium ($r = 0.80, p < 0.001$); and tumor volume and MBL ($r = 0.83, p < 0.001$) (Table 3). This confirms the findings of Purnell *et al.*[12]

Discussion

The importance of localizing hyperfunctioning parathyroid tissue preoperatively is obvious. Previously described methods of identifying neoplastic glands such as arteriography, venography and radioactive selenomethionine scanning have proven to be non-specific and prone to misinterpretation. Our data demonstrate the importance of radioimmunoassay measurement of PTH not only in the diagnosis of hyperparathyroidism but in the localization of the hyperfunctioning tissue. The measurement of PTH in the large veins (innominates, jugulars, and superior vena cava) gave data helpful in lateralizing the parathyroid neoplasm in half of our cases and these findings are comparable to observations reported by others. The streaming and dilutional effects which occur in these larger veins make them less accurate sampling sites than the thyroid veins which drain the parathyroid glands directly.

The radioimmunoassay of PTH in plasma samples from directly catheterized thyroid veins has offered a sensitive and specific method of localizing parathyroid neoplasms. In our 20 patients the presence of plasma PTH greater than twice MBL was associated with the presence of hyperactive tissue on the side where the elevation occurred. In patients with bilateral parathyroid hyperplasia gradients were present on both sides of the neck in all but one case. Although O'Riordan has been successful in predicting the actual parathyroid gland involved in about half of his cases we have been unable to determine which gland on a given side was involved or indeed if both were.

The importance of successfully catheterizing the inferior thyroid veins cannot be over-emphasized as this is the major route of parathyroid venous drainage and in most cases the highest values of PTH were measured in plasma samples from these veins. Occasionally, because of an anomalous venous pattern or ligation at previous operation, catheterization of the inferior thyroid veins is impossible. In those patients with previous neck surgery an arteriogram was performed initially so that veins could be more easily and accurately sampled at the subsequent selective venous catheterization. It is of prime importance that the radiologist and the surgeon review the arteriograms and the selective venous catheterization data to determine the specific sites of PTH elevation. Extensive operation with ligation of many of the thyroid veins might alter flow patterns making lateralization difficult. We observed this phenomenon in

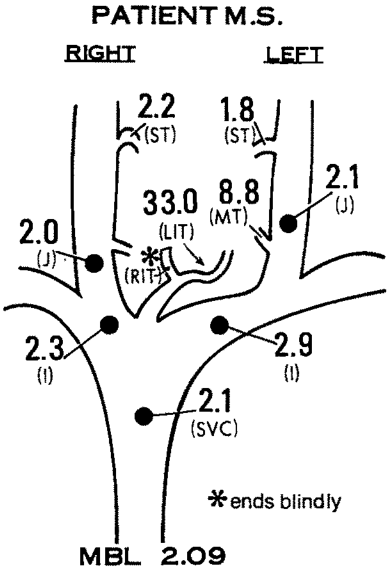

FIG. 3. PTH concentrations from selectively catheterized veins in patient M.S. who at previous operation had had a normal right lower parathyroid gland removed and the right lower pole vessels ligated. Plasma PTH levels of 33 ng/ml. were present in both the right inferior thyroid (RIT) and left inferior thyroid (LIT) veins. Venography showed a blind RIT and the high PTH on the right probably represents LIT blood which had refluxed into the RIT vein stump. At operation a left lower parathyroid adenoma was found. Normal right and left superior parathyroid glands were located.

two of the eight patients who had been operated upon previously.

It is this group of preoperative patients in whom the PTH radioimmunoassay of selective samples is of greatest value. The difficulties encountered in identifying structures in a previously explored neck are well known and the knowledge that a high PTH level is present on a given side enables the surgeon to concentrate his efforts there. We feel that the operative time has been shorter, the morbidity less, and the success of finding suspected lesions greater in patients since selective venous catheterization and PTH radioimmunoassay have become routine.

We do not feel that this technic is a substitute for a thorough exploration of the neck. In all cases every attempt was made to identify all parathyroid glands and confirm them as such by frozen section biopsy.

The measurement of PTH in plasma from selectively catheterized thyroid veins has been of great help in our series of 20 patients. It is hoped that it will be more widely used in the future.

Summary

Radioimmunoassay of plasma PTH from selectively catheterized thyroid veins and large neck veins was performed in 20 patients with primary hyperparathyroidism. In all cases a PTH level in the thyroid veins greater than twice the mean background level of PTH was associated with the presence of hyperfunctioning parathyroid tissue on the side where the elevation occurred. Unilateral PTH elevations were found in patients having single parathyroid adenomas while bilateral elevations occurred in all but one patient with bilateral parathyroid hyperplasia. The interpretation of the test results and the surgical significance of the technic are discussed.

Acknowledgment

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Management of Hemorrhage from Esophageal Varices Using the Esophagoscopic Sclerosing Method

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HEMORRHAGE from gastroesophageal varices is the most severe complication in patients with cirrhosis of the liver and portal hypertension. Approximately one-third of all patients with portal cirrhosis die of acute gastrointestinal hemorrhage.[2,4] There has never been a uniform concept of emergency management of variceal hemorrhage because of pitfalls in the surgical as well as the medical therapeutic technics. The major reason for the poor results of both therapeutic avenues lies in the decompensated liver function of most patients with variceal bleeding.

In patients with bleeding esophageal varices in whom reduced liver function rules against a decompressing shunt procedure, a number of alternatives are available. Palliative surgical procedures may be attempted but have a disadvantageous short hemostatic effect and a mortality rate which ranges as high as 50%.[2,4] The Sengstakem-Blakemore double balloon tube is frequently used successfully. Infusion therapy with vasopressin is often ill-advised because restriction of the microcirculation of the liver may lead to further decompensation of liver function and hepatic coma.

The double balloon tube is sometimes unsuccessful in the control of variceal hemorrhage, particularly when there are varicosities originating from the fornix region of the stomach. In addition, in patients who have congenital pre-hepatic blocks or cirrhosis with complete thrombosis of the portal vein, shunting is contraindicated despite good liver function values due to lack of a patent vein. Finally, in some patients thrombosis of a previously-functioning portal-systemic shunt may cause recurrent bleeding problems. The use of the endoscopic sclerosing technic is particularly applicable to the latter group of patients.

Materials and Methods

Acute hemorrhage from gastroesophageal varices was managed according to the following steps:

The initial effort consisted of blood replacement and insertion of the double balloon tube. In addition enemas and antibiotics were utilized to limit hepatic dysfunction. If control of hemorrhage was inadequate the esophagoscopic sclerosing treatment of varices, described by Wodak,[5] was carried out under general anesthesia. In most instances hemorrhage was arrested after the first sclerosing treatment. In instances of recurrent hemorrhage the double balloon tube was reinserted and the sclerosing therapy was repeated.

In the absence of acute hemorrhage, the following conditions constituted additional indications for use of the sclerosing procedure in patients with esophageal varices:

1. Decompensated liver function.
2. Pre-hepatic block in which splenoportogram failed to show patent vessels appropriate for a shunting procedure.
3. Thrombosed anastomoses between the portal and caval system.

The technic used for the sclerosing therapy was originally described by Crawfoord and Frenckner[1] and later

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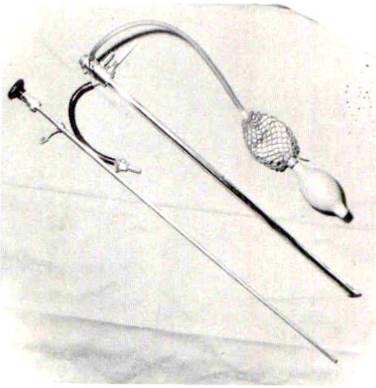

FIG. 1. Instrument for the sclerosing therapy of varices in the terminal esophagus.

modified by Wodak.[5] Following anesthesia by orotracheal intubation the esphagoscope was inserted. This instrument included an optical system which permitted a detailed enlarged view of the entire inner surface of the esophagus (Fig. 1). After the varices had been visualized, a magnifying optical device was introduced which included a 12-gauge cannula. The cannula was inserted into the submucosa adjacent to the varices (Fig. 2). Then a maximum of 2 ml. of 5% Varicocid* was injected into the submucosa at each selected site.

The total volume of Varicocid did not exceed 10 ml. Following injection, a small hemorrhage appeared at the site of injection which usually stopped by the end of the procedure. When bleeding continued, slight compression was applied using an adrenalin-soaked sponge. When severe hemorrhage occurred a supplementary suction device was inserted to remove the clotted and fresh blood. To achieve optimal results the procedure had to be performed quickly and the injections had to be accurately placed. When performed during acute hemorrhage, the sclerosing technic was performed with close monitoring of pulse and blood pressure. A large bore intravenous catheter was placed to facilitate immediate and rapid transfusion when needed.

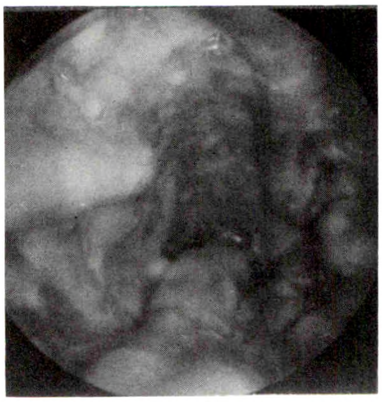

FIG. 2. Picture of varices in the terminal esophagus.

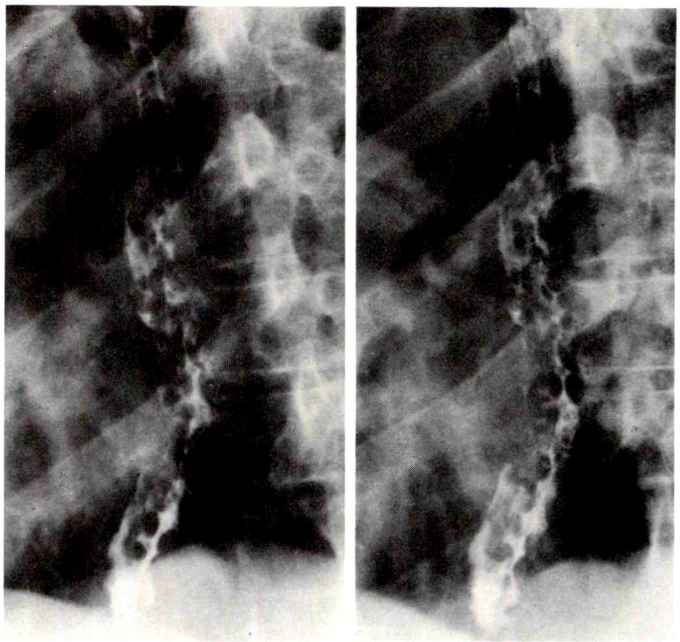

FIG. 3A. X-ray of the esophagus before sclerosing therapy in an acute (bleeding) instance.

The endoscopic sclerosing procedure could be repeated at 3-day intervals. After three to four sessions an upper gastrointestinal radiographic series demonstrated the results.

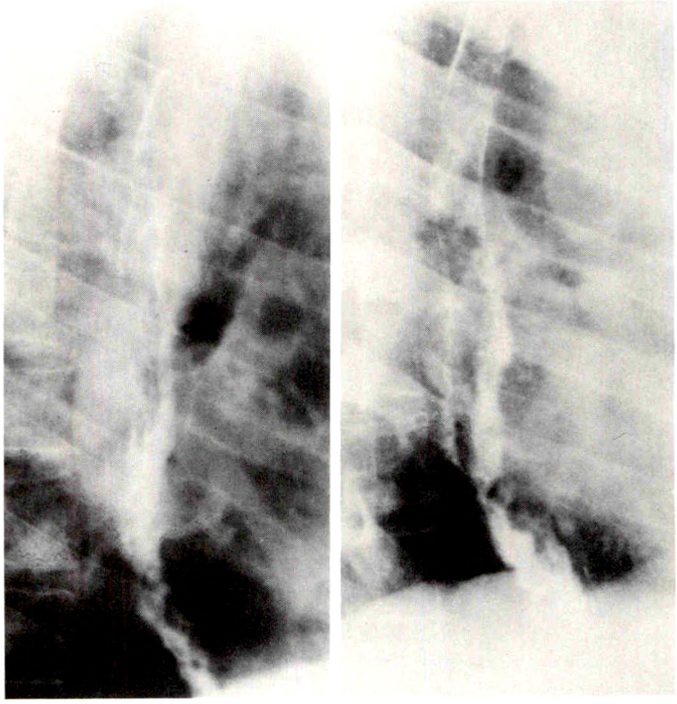

FIG. 3B. X-ray of the esophagus after therapy.

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* Varicocid is produced by the Combustinwerke Eulitz Co., 8031 Saefeld/066, Germany and consists of alkaline salts of the fatty acids of cod-liver oil and 2% benzyl alcohol in 5% solution.

Results

A total of 30 patients were treated with this technic—12 during acute hemorrhage and 18 during a free interval.

The acute hemorrhage was caused in nine instances by portal hypertension and cirrhosis. One of the patients bled on the fifth postoperative day after distal splenorenal shunt. In two other patients the shunts had thrombosed.

The remaining 18 cases included the following: 13 patients with decompensated cirrhosis, one patient with a thrombosed proximal splenorenal shunt, two patients with thrombosed mesocaval shunts, and two patients who had undergone splenectomy and had thrombosed portal veins (Table 1).

In all but one of the patients, the sclerosing therapy immediately controlled hemorrhage and radiologically a decrease in varicosities was demonstrated.

Six of the patients with acute hemorrhage died. Causes of death included: hepatic coma in four patients, myocardial infarction with aneurysm in one, and necrosis of the terminal esophagus with pyothorax in one.

Of the 18 patients treated during a free interval, 4 died in hepatic coma and in two instances hemorrhage from varices in the fornix could not be stopped (Table 2).

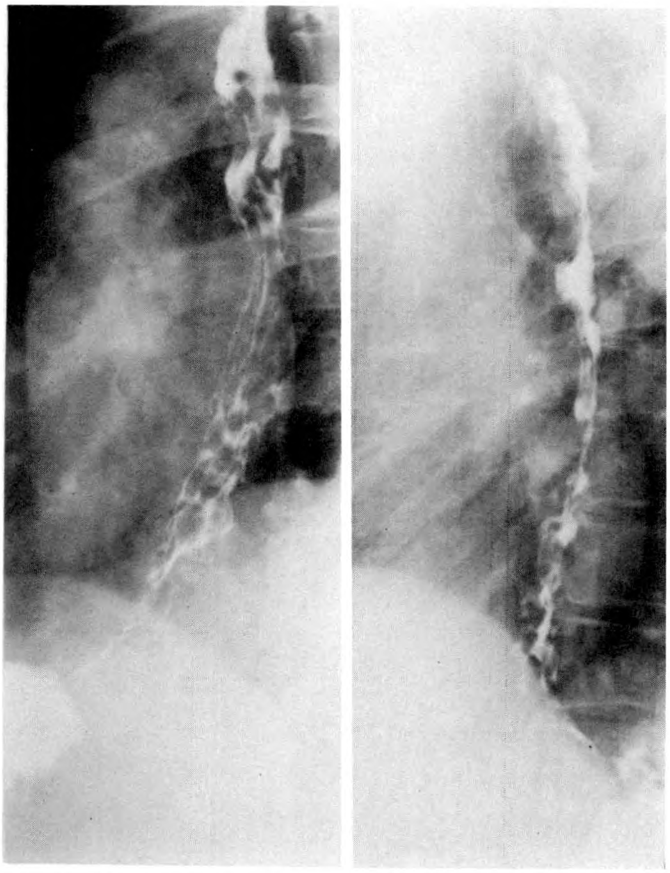

FIG. 4A. X-ray of the esophagus before sclerosing therapy in a chronic case, *i.e.* the interval free of hemorrhage.

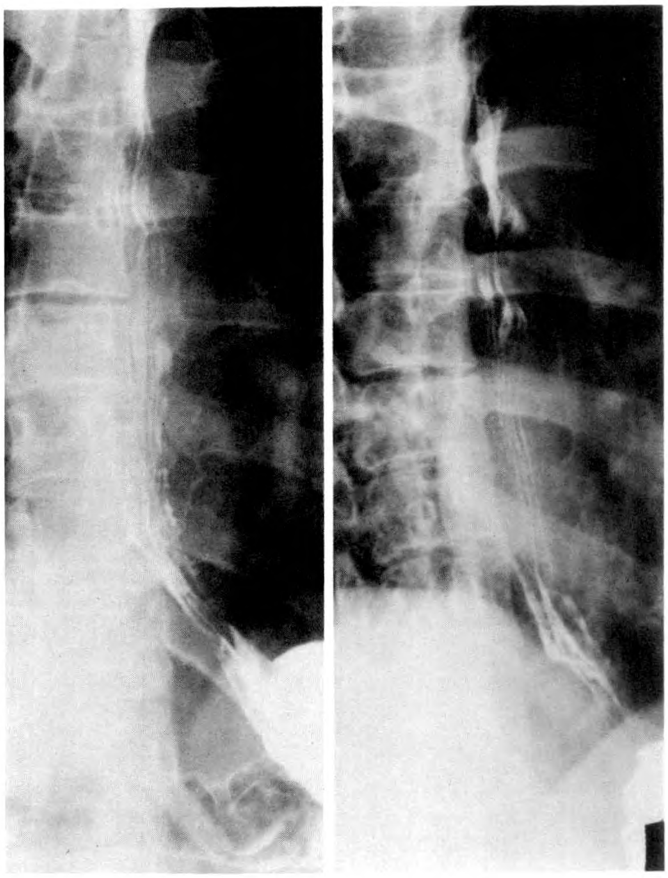

FIG. 4B. X-ray of the esophagus after therapy.

Eighteen patients were alive after the final sclerosing treatment for periods ranging from 3 months to 3 years.

Discussion

Sclerosing of esophageal varices is applicable in a variety of clinical situations. When used during massive,

TABLE 1. *Diagnosis of the 30 Cases of Gastroesophageal Varices Managed Using the Esophagoscopic Sclerosing Method.*

I. Acute bleeding from gastroesophageal varices (12 cases)	
1) Decompensated liver cirrhosis with portal hypertension:	9
2) Thrombosed portocaval shunt (liver cirrhosis):	1
3) Thrombosed splenorenal shunt (liver cirrhosis):	1
4) Splenorenal shunt without thrombosis six days after operation (liver cirrhosis):	1
II. Gastroesophageal varices during the interval free of bleeding (18 cases)	
1) Decompensated liver function with portal hypertension:	13
2) Thrombosed mesenteriocaval shunt:	
prehepatic block:	1
liver cirrhosis and portal vein thrombosis:	1
3) Splenectomy and portal vein thrombosis:	2
4) Thrombosed splenorenal shunt (prehepatic block):	1

TABLE 2. *Mortality of 30 Patients following the Endoscopic Sclerosing Therapy of Esophageal Varices. Twelve Patients Were Treated during the Acute Hemorrhage and 18 Patients in the Free Interval.*

I. *Acute cases: 6*	
1) Liver coma:	4 cases
2) Cardiac infarction:	1 case
3) Necrosis of Esophagus.	1 case
II. *Chronic Cases 6*	
1) Liver coma:	4 cases
2) Hemorrhage from gastric varices	2 cases

uncontrollable variceal hemorrhage, it permits immediate hemostasis in almost all instances. The sclerosing technic is also used during the "free interval" in patients with decompensated liver function, in instances of shunt occlusion and in patients with pre-hepatic block, in whom shunting is anatomically impossible. In these patients, remission of the varices can be demonstrated by upper gastrointestinal radiography. Endoscopically, the technic results in a thickening of the esophageal mucosa, covering the site of the varices, and prevents further bleeding.

Since this technic is purely a palliative measure, and does not in anyway decompress the portal system, the patients must be evaluated clinically and radiologically at 3- to 6-month intervals. If hemorrhage recurs or the varicosities increase, the sclerosing therapy must be repeated. The method is not applicable to paraesophageal or gastric varices.

Complications of this technic include acute hemorrhage from gastric varices, and necrosis of the esophagus. The latter may be partly the result of lesions caused by pressure when the Sengstaken tube is used before o after sclerosing. Careful procedural technic can minimize the incidence of the latter complication.

Summary

The technic of sclerosing the wall of the esophagu for treatment of bleeding varicosities of all origins ha proven useful because of its hemostatic and thus lifesaving results during acute hemorrhage. When shun procedures are not feasible because of poor hepati function or anatomical abnormalities, the sclerosin therapy can be applied during the "free interval." Disadvantages of this palliative technic include the enhancement of life-threatening hemorrhage from gastri varices and the necessity for careful follow-up study Sometimes repeated sclerosing injections are necessar according to the findings at follow-up studies performe at regular intervals.

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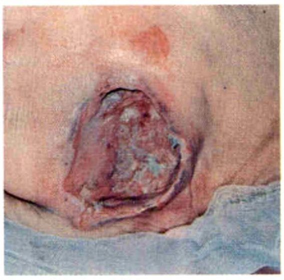
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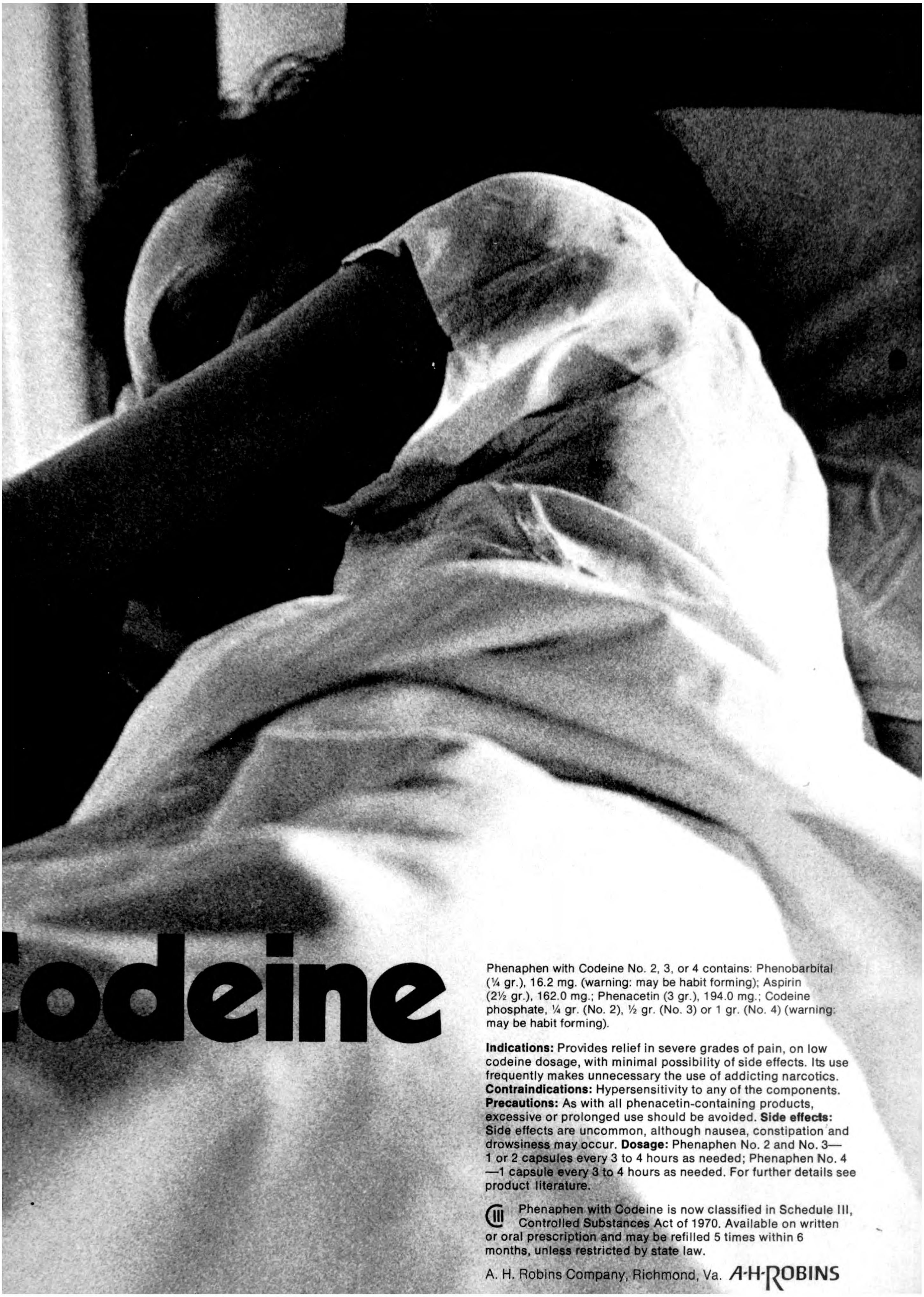

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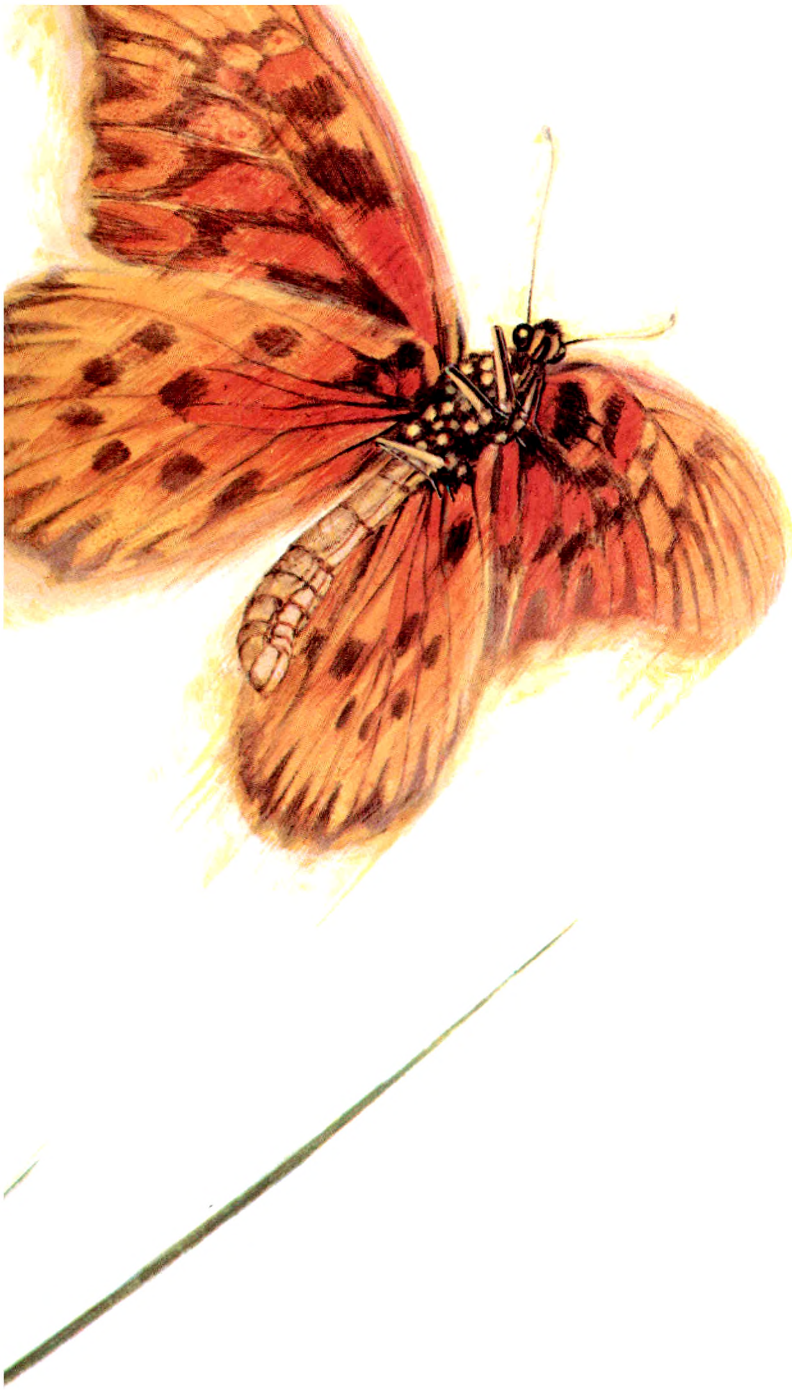

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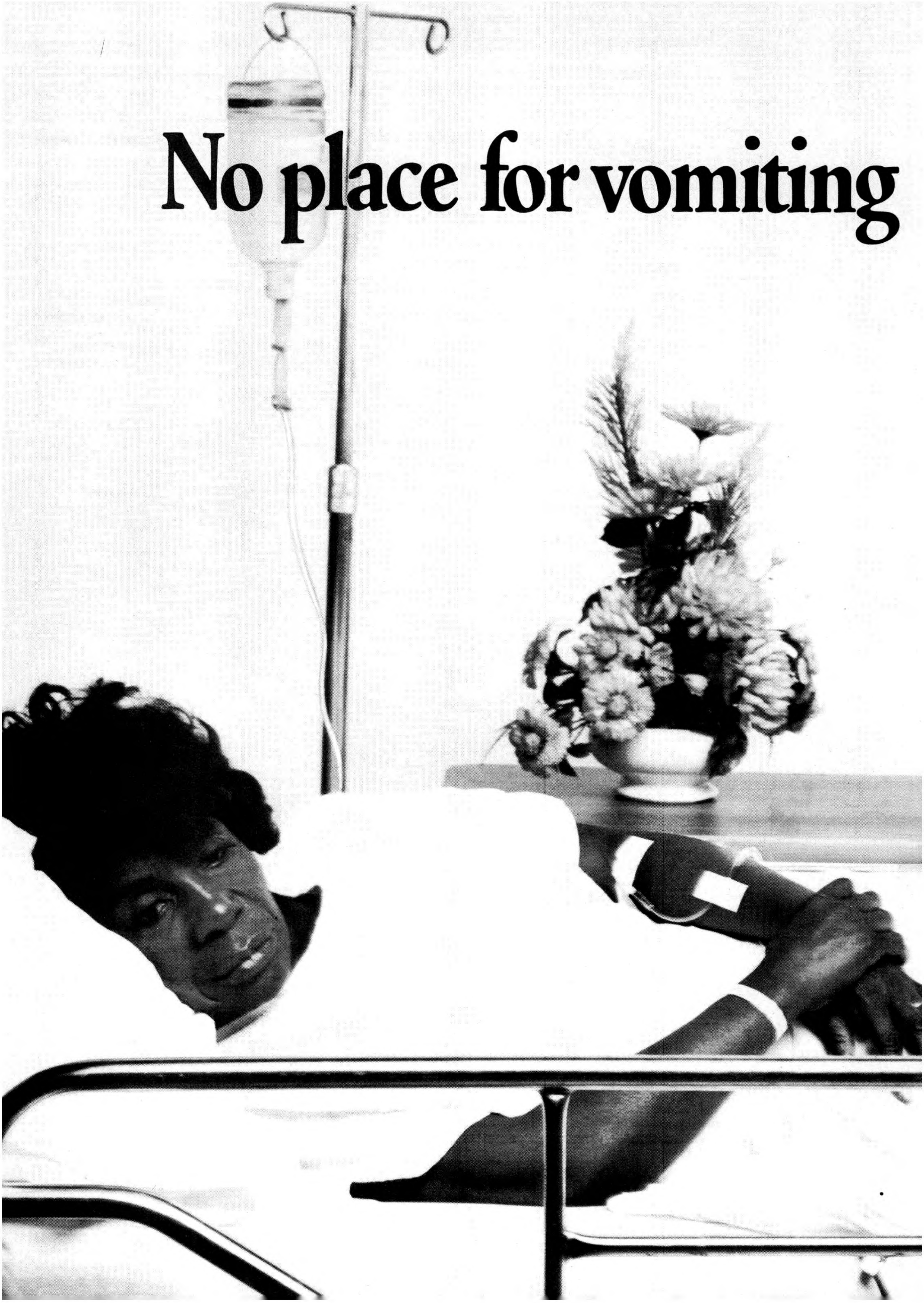
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Diagnose this unusual case in gastroenterology

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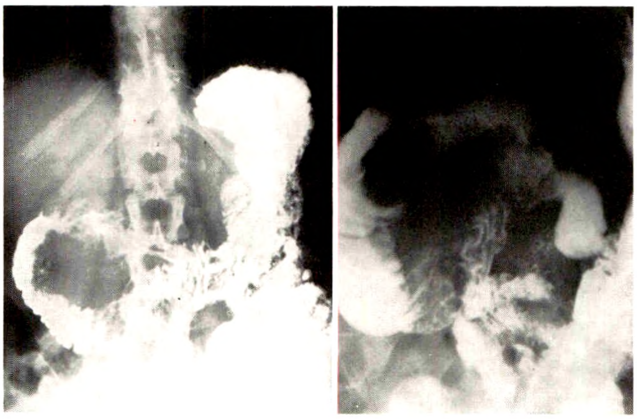
The problem: The patient is a 59-year-old female with a history of relatively good health, early satiety followed by dizziness, weight loss and steatorrhea of three weeks' duration. Initial x-rays were interpreted as being consistent with pancreatic carcinoma.

The case: Three weeks prior to admission to the Gastrointestinal Division of University of Miami Hospital, the patient complained that after eating a large evening meal and going to bed, she awoke in the middle of the night feeling dizzy. Since that episode, her consumption of food was decreased and she was able to digest what she ate despite a feeling of satiety and a particular *notice* of fullness in the epigastrium. Her intermittent stools had a foul odor and *urine became light in color and remained clear and normal in color.* There was no apparent jaundice or overt melena.

Physical examination limited to the abdomen showed no fixed hepatosplenomegaly. There was a suggestion of a nontender mass apparently fixed in mid-abdomen. Rectal examination was normal. Laboratory study showed mild anemia. X-rays of the upper GI tract revealed a marked deformity of the duodenal bulb and regular defects with a double-wall defect in the projection of the duodenal bulb and duodenal loop, highly suggestive of carcinoma of the pancreas. Pancreatic scan disclosed decreased activity in the head and body of the pancreas interpreted as possible carcinoma. Liver scan showed focal defects highly suspicious of metastatic lesions.



Your diagnosis, Doctor? ____________________

On the following page, compare your diagnosis with that made by Martin Kalser, M.D.

Professor of Medicine
and Physiology,
Chief, Division of
Gastroenterology,
University of Miami
School of Medicine,
Coral Gables, Florida

One in a series of case
histories in gastroenterology
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Diagnosis of a problem in gastroenterology

by Martin Kalser, M.D.

(case history on preceding page)

Discussion: The problem in this case was that the roentgen findings and abnormal pancreatic and liver scans (indicating metastases) were thought to be consistent with diagnosis of a primary carcinoma of the head of the pancreas with invasion of the duodenum and metastases to the liver. Duodenoscopy disclosed a fungating, polypoid lesion, friable in the duodenum that looked like an adenocarcinoma. On exploration, following test biopsy, a large, hard mass, posterior to the duodenum was found. Frozen section showed the primary lesion to be a fungating, frond-like neoplasm, involving the first and second portions of the duodenum which had perforated posteriorly. The perforation exited from the duodenal wall into the pancreas and there was an abscess cavity posterior to the pancreas. A gastrojejunostomy was performed and abscess drained. The liver was found to have multiple, small, smooth wall cysts which were entirely benign. There was no evidence of any metastases grossly.

Conclusion: Although adenocarcinoma of the duodenum is rare, it should be considered in lesions involving the second portion of the duodenum when examination and laboratory findings show atypical manifestations. A particular feature in this case is the presence of anemia, indicating slow bleeding, and a normal liver profile. This finding would be highly improbable in either carcinoma of the head of the pancreas or carcinoma of the ampulla of Vater. The latter may cause anemia but would not in any case be associated with a normal liver profile. The value of duodenoscopy in diagnosing lesions of the stomach and duodenum may be more valuable, or just as valuable, as specialized x-ray procedures.

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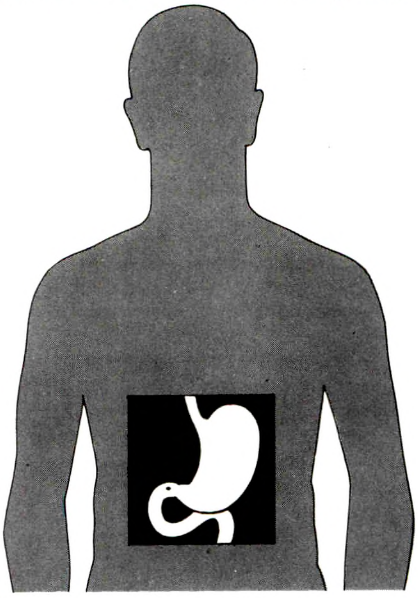

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An Assessment of the Role of Parenteral Alimentation in the Management of Surgical Patients

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HAROLD H. SANDSTEAD, M.D.***

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IN RECENT YEARS, the role of nutrition in the management of surgical patients has been extensively reappraised. Patients undergoing major operative procedures, or those with burns or other major trauma, have nutritional requirements far in excess of what can be given with conventional intravenous fluid therapy. In an effort to meet these requirements, the use of total parenteral alimentation (TPA) has been investigated in a number of institutions.[2,7,8,10,17,18,24]

Between 1969 and 1971, a total of 102 patients have been given TPA at Vanderbilt University Hospital as an adjunct to surgical treatment of the underlying diseases (Table 1). The present communication summarizes what has been learned from this experience about the management of surgical patients with total parenteral alimentation using crystalline amino acids as the sole source of nitrogen.

Materials and Methods

Indications for TPA and Patients Studied

Table 1 shows the type of patient in whom TPA has proved to be valuable. TPA is indicated in patients with excessive nutritional depletion because of disease or surgical treatment. Three types of situations are particularly noted. The first is the debilitated patient who must undergo a major operative procedure. A weight loss of 5 to 10 Kg. or more is common after major operations. This is associated with a nitrogen loss of 5 to 15 Gm. per day which reflects extensive net protein breakdown. While this can be tolerated by an adequately nourished young man, marked catabolism in the elderly or nutritionally depleted individual may be difficult to overcome. TPA provides a means for supplying the extraordinary requirements of the postoperative period. The phase of negative nitrogen balance seen postoperatively can be minimized or even eliminated with TPA.[20]

The second situation is seen in patients who have had multiple trauma or burns. In such patients, the metabolic requirements far exceed those found in postoperative patients. The patient with multiple fractures may have a nitrogen loss exceeding 25 Gm. per day for 1 or 2 weeks, and the patient with severe burn injury may lose 30 to 40 Gm. of nitrogen per day. The basal metabolic expenditure may be 150 to 200% of normal.[14] It is common to see such a patient lose 15 to 25 Kg. during the course of a 6-week hospitalization. It is possible to treat such a patient without regard to nutritional requirements, but the survivors will leave the hospital gaunt and emaciated, with the stigmata of protein-calorie malnutrition.

The patient with widespread carcinoma is often referred for treatment with TPA. These patients are usually losing weight and may be anorexic. Chemo- or radiotherapy would aggravate their deteriorating condition. As can be seen from Table 1, three patients have been treated with TPA in conjunction with chemotherapy.

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TABLE 1. *Diagnosis and Number of Patients Given Parenteral Nutrition*

Diagnosis	Number of Patients
Postoperative	47
Bowel Resection	18
Gastric Resection	15
Biliary Tract	7
Liver Resection	3
Aortic Aneurysm Resection	3
Laryngectomy	1
Trauma	20
Burn	10
Multiple Trauma	10
Obstruction	17
Regional Enteritis	8
Intestinal Fistula	7
Esophageal Obstruction	2
Other	18
Terminal Malignancy	8
Carcinoma with Chemotherapy	3
Miscellaneous	7
Total	102

This particular combination has proved beneficial, permitting patients to be given larger doses of chemotherapeutic drugs than can be given to those dependent upon oral nutrition.

Composition and Preparation of Infusate

Calories, protein, vitamins, electrolytes and water must be provided in optimum proportions. Administration of a single, "standardized" solution containing amino acids and adequate calories along with electrolytes and vitamins has been found very satisfactory for two reasons. First, it facilitates preparation and distribution of the infusate. A "standard" solution can be made up by batch processing, as will be discussed later. Second, it has been shown that nitrogen as protein hydrolysate or crystalline amino acids must be given with calories to prevent the utilization of the amino acids for energy. Only if the amino acids are given with adequate calories will positive nitrogen balance be achieved.[9]

Caloric requirements can be met by carbohydrates and fat. Fat emulsions are used widely in Europe, but have not undergone sufficient clinical trial in this country to be released for general use.[2,13,17] A soybean oil emulsion, Intralipid®, is currently under clinical investigation. The carbohydrate solutions include the polyols, alcohol and sugars (glucose, fructose and invert sugar). While the polyols (sorbitol and xylitol) may have some theoretic advantages over the sugars, their use in this country has been limited.[17] Alcohol, with its high caloric content of 7 kcal. per Gm., has been used for parenteral alimentation. However, its long-term effects, especially in infants and children, remain poorly understood. Of the sugars, glucose has been most widely used. It is physiologic, readily utilized by the body, and its metabolism is well understood. However, intravenous administration of hypertonic glucose solutions produces a high incidence of thrombophlebitis unless the solution is infused into a large central vein. Hyperglycemia may be encountered in many patients unless insulin is given concomitantly. Despite the difficulties encountered, it remains a satisfactory method for providing calories. Generally 2500 to 3000 kcal. must be given to the average patient under moderate metabolic stress and 4000 kcal. or more to the patient under severe stress.[14,16,17]

Nitrogen requirements may be met by the use of protein hydrolysate or by crystalline amino acid solutions. Protein hydrolysate is satisfactory; the disadvantage is that it contains di-, tri-, and perhaps tetrapeptides in the preparation. Peptides are probably not as efficiently utilized as crystalline amino acids for protein synthesis. Since crystalline amino acid solutions are now available which can be made up to optimum compositions and which are totally utilizable by the body, protein hydrolysate has not been used at Vanderbilt University Hospital. The composition of the amino acid solution which has been employed in this group of patients is shown in Table 2.

Vitamin requirements in the metabolically stressed patient are poorly understood. The vitamin composition of the solutions used in our patients is shown in Table 3. This represents an approximation to the requirements and has proved satisfactory. Vitamin K has not been incorporated into the solutions and was given separately when needed.

Electrolyte requirements vary considerably from patient to patient. As shown in Table 3, standard amounts of sodium and potassium have been included. The amount per day of 70 mEq of sodium and 120 mEq of potassium has been satisfactory for most patients and can be adjusted for special needs. There are two reasons for the rather large potassium requirements. First, pa-

TABLE 2. *Composition of Amino Acid Solution**

Amino Acid	Gm./100 ml.	Amino Acid	Gm./100 ml.
L-Isoleucine	0.59	L-Alanine	0.60
L-Leucine	0.77	L-Arginine	0.31
L-Lysine·HCL	0.77	L-Histidine	0.24
DL-Methionine	0.45	L-Proline	0.95
L-Phenylalanine	0.48	L-Serine	0.50
L-Threonine	0.34	L-Cysteine·HCL·H_2O	0.02
L-Tryptophan	0.13	Glycine	1.79
L-Valine	0.56		

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Amino Acid—8.5 Gm./100 ml.
Nitrogen—1.25 Gm./100 ml.
Alpha Amino Nitrogen—1.06 Gm./100 ml.
Protein Equivalent—7.8 Gm./100 ml.

TABLE 3. *Daily Nutrients Given in Three Liters T. P. A.—900**

Nutrient	Amount	Vitamin	Amount
Water	3000 ml.	Vitamin A	3300 Units
Dextrose	750 Gm.	Vitamin D	330 Units
Amino Acids	85 Gm.	Vitamin C	165 mg.
Nitrogen	12.5 Gm.	Vitamin E	1.65 Int. Units
Protein Equivalent	78 Gm.	Thiamine HCl (B_1)	16.5 mg.
Calories†	2700 kcal.	Riboflavin (B_2)	3.3 mg.
Sodium	70 mEq	Pyrodoxine HCl (B_6)	4.95 mg.
Potassium	120 mEq	Niacinamide	33 mg.
Magnesium	30 mEq	Panthenol	7.25 mg.
Chloride	105 mEq	Folic Acid	300 μg
Acetate	155 mEq	Vitamin B_{12}	30 μg
Zinc Sulfate	15 mg.		

* T. P. A.—900—Total Parenteral Alimentation supplying 900 kcalories per liter.
† Non-protein calories.

tients under stress tend to have a large urinary potassium loss, presumably because of hypersecretion of aldosterone. Second, the administration of large amounts of glucose and the occurrence of intracellular protein synthesis both increase the intracellular potassium pool. Magnesium, another intracellular electrolyte which serves as a co-enzyme, was also provided (30 mEq/day). Magnesium deficiency in patients under stress occurs commonly but is rarely recognized.[15] Calcium was not provided because of the tendency of calcium salts to precipitate out of the infusate and must be given separately. However, 10 mEq of calcium as calcium gluconate (10%) and 6 mEq of phosphorus as a mixture of dibasic and acid potassium phosphate could be safely added to 1 liter of infusate. Phosphorous deficiency has been reported recently.[25] A daily dose of 10 mEq or 300 mg. of inorganic phosphorous has been recommended.[27] Of the inorganic trace elements, zinc was included in the infusate. Iron has not been added and was given separately when needed.

Water requirements vary widely. About 3000 ml. per day was satisfactory in most adult patients. Additional needs were supplied separately.

Table 3 summarizes the composition of the infusate presently employed. The standard solution, TPA-900, was designed to provide 900 kcal. and 4.17 Gm. of nitrogen; thus, 3000 ml./day would supply 2700 kcal. with 12.5 Gm. of nitrogen. A more concentrated solution, TPA-1150, was used in patients with additional caloric requirements and provided 3450 kcal. and 12.5 Gm. of nitrogen in 3000 ml. of fluid. A still more concentrated solution, TPA-1600, was designed for patients with severe restrictions on fluid intake, such as those with renal failure, and provided 1600 kcal. and 6.25 Gm. of nitrogen with 1000 ml. of fluid.

The solution for parenteral nutrition used in infants and children is TPA-I-900 which contained 20% carbohydrate as 10% glucose and 10% fructose and 0.42% nitrogen as crystalline amino acids. One liter of TPA-I-900 furnished 100 Gm. glucose, 100 Gm. fructose and 4.2 Gm. nitrogen or 26 Gm. protein equivalent along with the following electrolytes: sodium-25, potassium-30, magnesium-10, calcium-10, chloride-25.5, acetate-27, lactate-3, mEq and zinc sulfate-10 mg. Four c.c. MVI, 1 mg folate and 100 μg B_{12} were added to 1 liter of TPA-I-900.

All preparation of these solutions was carried out by the hospital pharmacy. Figure 1 shows the type of apparatus used. The solution was prepared in 5 gallon batches. The sterile solutions of amino acids, glucose, electrolytes and vitamins were added, mixed and bottled through a Millipore filter (pore size-0.22 μ) under nitrogen in a closed system. The TPA solution was then capped, labeled and sampled at random for sterility and pyrogenicity tests before release for infusion in patients. Bottles were discarded 12 hours after the seal was broken. All intravenous infusion sets were changed daily. Meticulous care of the infusion site was emphasized. No medications were added to the bottles of TPA infusate,

TABLE 4. *Balance Studies and Caloric Intake on J. H.*

	Average Daily Intake and Output												
	Calorie	Nitrogen (Gm.)			Sodium (mEq)			Potassium (mEq)			Fluid (cc)		
Day	Intake	In	Out	Bal.	In	Out	Bal.	In	Out	Bal.	In	Out	Bal.
1-10	3020	13.5	29.3	15.8	83.0	61.7	21.3	92.8	65.5	27.3	5343	2193	3150
11-35	4684	16.5	19.9	13.4	206.6	81.2	125.4	145.6	80.0	66.6	5161	2621	2540
1-35.	4137	15.4	21.7	16.3	172.5	75.8	96.7	131.8	76.0	55.8	5213	2714	2499

TABLE 5. *Serum Electrolytes, Urea, and Glucose and Plasma Osmolality (J. H.)*

Date	Serum Electrolytes (mEq/L) Na	K	Cl	CO$_2$	Urea mg./100 ml.	Glucose mg./100 ml.	Plasma Osmolality (mOsm/L)
June 3, 1971	141	3.1	102	28.5	21	—	—
5	133	3.8	102	24.5	14	—	—
8*	135	4.5	111	18.5	18	196	—
10	144	4.5	113	21.0	25	160	303
12	145	4.5	116	21.5	21	156	313
14	135	4.9	115	21.0	21	214	300
17	132	4.7	108	17.5	18	127	295
20	133	4.2	105	22.5	14	288	289
24	133	3.7	103	22.5	15	80	291
8	127	4.1	98	23.5	10	186	277
July 21	132	4.3	99	25.0	14	98	270
4	138	4.1	108	23.0	7	231	—
7	137	4.2	107	21.5	13	316	307
10	145	3.4	109	25.0	14	252	300
13	139	3.5	108	24.5	17	220	316
15	136	3.1	109	25.0	23	158	308

* TPA started on June 8 and discontinued on July 12, 1971.

save for electrolytes, which were added in the pharmacy under a Laminar-air flow hood. Use of these precautions has virtually eliminated the problem of contamination of TPA infusate in our experience.[6]

Administration of Infusate

TPA solution was delivered into the superior vena cava by way of an indwelling catheter. When possible, 3 liters per day were given continuously at a rate of 125 ml./hour. The total volume of TPA solution given per day varied from patient to patient depending on the condition of the individual subject. It was our practice to administer 1 liter on the first day, 2 liters on the second, and 3 on the third and succeedings days. In infants and children, the volume of TPA-I-900 administered was usually 125 ml./Kg./day continuously through an inline Millipore filter (0.22 μ) which was aided by a pump.

Balance Studies

Whenever possible, patients receiving TPA were maintained on balance studies. Complete records of parenteral and oral, if any, intake were kept. Continuous urine, gastric or intestinal aspirate collections were maintained. Continuous stool collections were also made in some cases. Urine, gastric and/or intestinal secretions and stools were measured for volume or weight and analyzed for nitrogen, sodium, potassium and magnesium. Oral intake of food was also analyzed for electrolytes, nitrogen and fat; caloric content was then calculated. While stool collections were not always feasible, it was found that stool nitrogen losses were less than 10% of the urine losses and considerably less than 10% in patients receiving no oral intake. These data allowed calculation of caloric intake and fluid, nitrogen, sodium, potassium and magnesium balances on a daily basis.

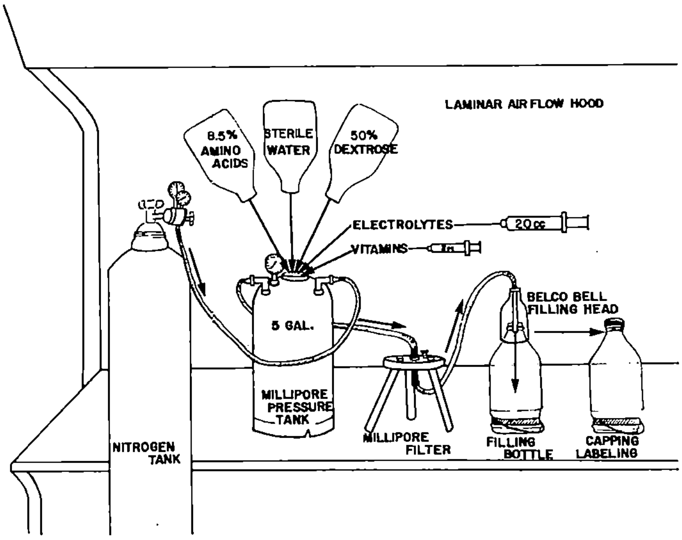


FIG. 1. Preparation of solution for total parenteral alimentation.

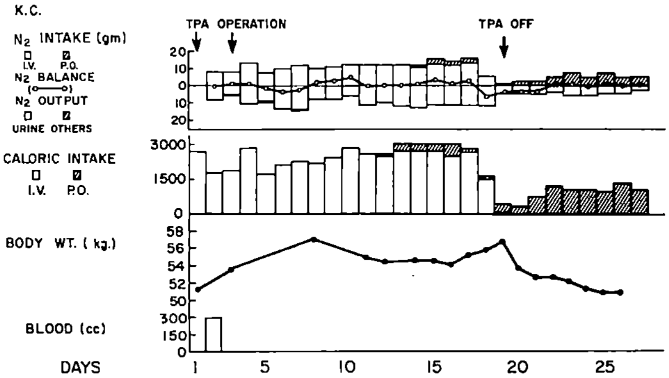


FIG. 2. Caloric intake, body weight, and nitrogen balance in K. C

Results

The results obtained from four patients of the group are presented herein. Each serves to illustrate one particular aspect of the use of TPA in patient management.

Case Reports

Case 1. K.C., a 74-year-old woman, was admitted to Vanderbilt University Hospital on October 31, 1969, with a 6-month history of vague epigastric pain. She was thin and debilitated and was found to have a large gastric mass. Total parenteral alimentation was begun 2 days before and continued for 16 days after operation. At exploration she was found to have a large gastric lymphosarcoma. She underwent a total gastrectomy, splenectomy, distal pancreatectomy, partial colectomy and gastric replacement with a Hunt-Lawrence pouch.[21,22] Postoperative course was smooth, although insulin was required for control of hyperglycemia. Figure 2 shows her daily caloric intake, body weight and nitrogen balance. She was in negative nitrogen balance of 5 Gm. or less on the second, third and fourth days. With an average daily nitrogen and caloric intake of 11.6 Gm. and 2449 kcal., respectively, she gained a total of 6 Kg. during the period on TPA. She lost most of the weight gained after being taken off total parenteral alimentation. Figure 3 shows the fluid, sodium, potassium and magnesium balance. It can also be seen that nitrogen and potassium balances correlated with each other. Magnesium was always in positive balance. The sodium balance was variable depending for the most part on intake. Fluid balance was always positive. She left the hospital weighing more than she did on admission. At follow-up examination 7 months later, she was found to have maintained her weight and was clinically well.

This patient was benefited by the use of TPA. She withstood an extensive surgical procedure and gained weight while on parenteral nutrition therapy. In addition, only a slight negative nitrogen balance was observed on the 2nd, 3rd and 4th postoperative days. Despite the nitrogen loss, a net average daily nitrogen retention of 0.52 Gm. was achieved during the 15 days following operation. The short postoperative period of negative nitrogen balance was, in part, due to difficulties encountered in regulating her insulin dosage. The need of exogenous insulin in this patient was undoubtedly due to her age and partial pancreatectomy rendering the endogenous secretion of this hormone inadequate. The subsequent weight loss of about 4 Kg. observed after TPA was discontinued was due, in part, due to inadequate oral food intake and perhaps some water loss. While this may represent excess body water, frank edema or symptoms of circulatory overload did not occur in this patient.

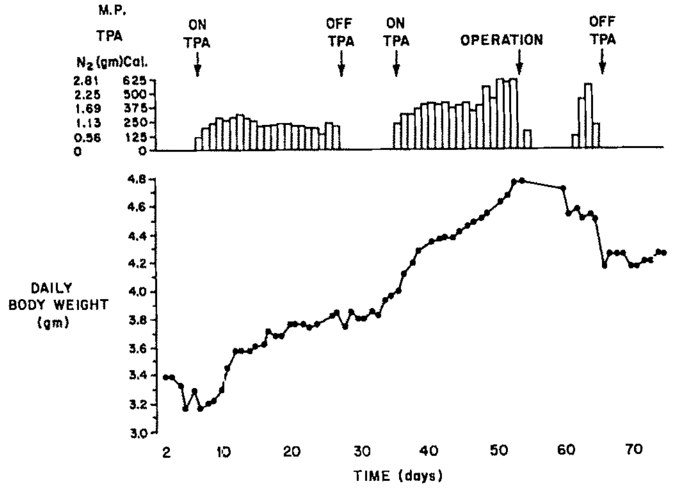


FIG. 4. Caloric and nitrogen intake and weight in M. P.

Case 2. M.P. was a 4-day-old girl with a birth weight of 3.1 Kg. She was admitted to Vanderbilt University Hospital on August 29, 1970 with respiratory difficulty and vomiting. She underwent removal of a pulmonary sequestration of the left lower lobe, closure of a fistula between the bronchus of the sequestered lobe and the esophagus, and repair of a hiatal hernia associated with a congenital short esophagus. She recovered well and was discharged 3 weeks after operation. She failed to gain weight and experienced frequent vomiting. At the age of 3 months she weighed 3.4 Kg., a gain of only 0.3 Kg. since birth. She was re-

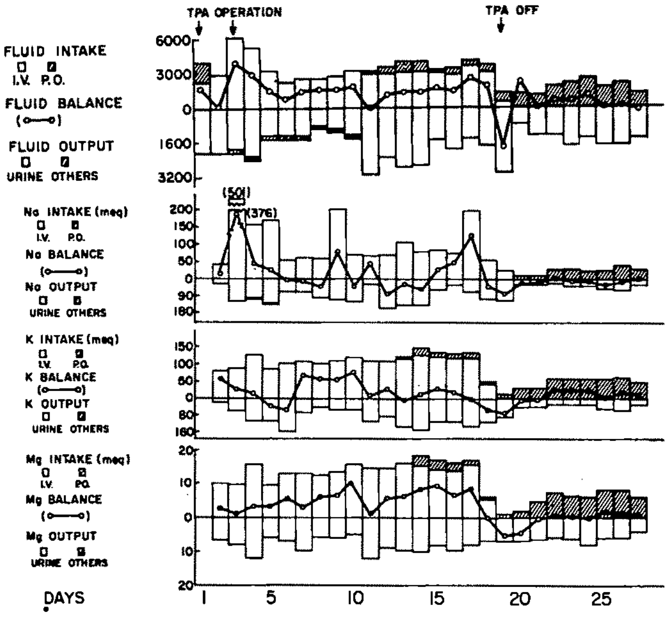
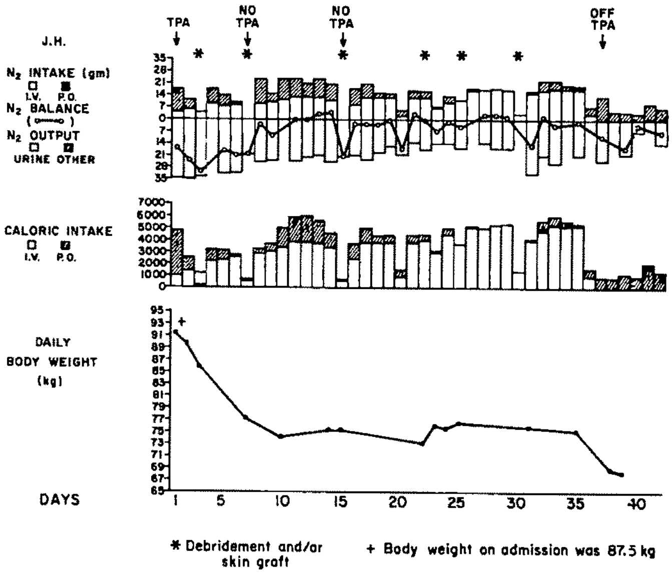


FIG. 3. Fluid, sodium, potassium, and magnesium balance in K. C.



* Debridement and/or skin graft + Body weight on admission was 87.5 kg

FIG. 5. Caloric intake, body weight, and nitrogen balance in J. H.

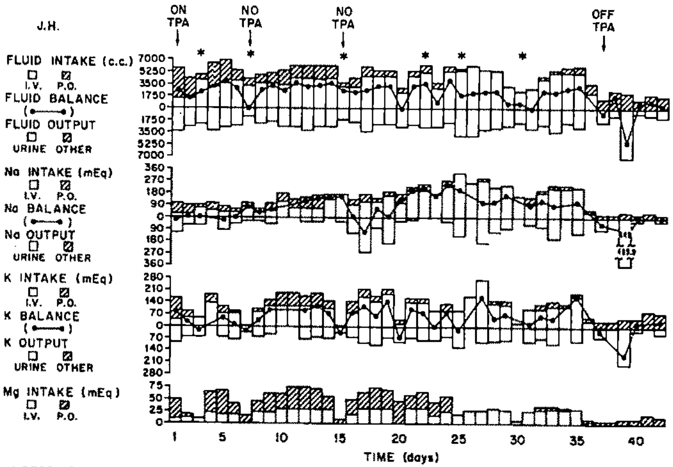


FIG. 6. Fluid, sodium and potassium balance and magnesium intake in J. H.

admitted to the hospital on November 24, 1970 and was placed on TPA. As can be seen in Figure 4, the patient was maintained on TPA for 44 days during a period of about 2 months with 2 periods of interruptions. She gained weight satisfactorily. After 21 days of TPA, oral feeding was attempted but the child's intake was small. After 9 days of unsuccessful oral feeding, TPA was reinstituted. It can be noted in Figure 4 that the body weight curve leveled during this period of inadequate food intake. The second course of TPA lasted for 18 days. At the end of this period, her body weight was about 4.8 Kg., a gain of 1.6 Kg. during a period of 38 days including the 9 days of unsuccessful oral feeding. It was felt at this time that the patient could withstand an anticipated surgical procedure which was performed on February 1, 1971. The operation was a resection of distal esophagus with interposition of a segment of jejunum between the esophagus and the stomach, a Heineke-Mikulicz pyloroplasty, and splenectomy. TPA therapy was begun on the first postoperative day. However, it was interrupted because of the difficulty encountered in maintaining the central venous catheter; the patient was maintained on a conventional fluid therapy for 7 days after which TPA was again given. The central venous catheter was dislodged 4 days later. Since she was able to tolerate oral feeding, TPA was discontinued. She continued to increase her oral intake and was discharged 3 weeks after operation. She has done well since, with weight gain and development, although she remains somewhat below normal weight for her age.

This child had a very complex set of anomalies and still has a congenital heart defect, situs inversus totalis and residual feeding difficulties. She would unquestionably have succumbed without the use of TPA. The operative procedure on February 1, 1971 would have been impossible to perform on a small, emaciated child.

Case 3. J. H. A 28-year-old chemical plant worker was admitted on June 3, 1971 with phosphorous burns of 70% of the body surface involving the trunk and all four extremities. About 30% of the body had full-thickness skin loss. After stabilization of the initial fluid and electrolyte imbalances, he was placed on TPA 6 days after burn as part of a program of nutritional supplementation which also included oral feedings of hospital diets and oral and tube feeding of an elemental diet (Vivonex-100). Figure 5 shows the daily caloric intake, nitrogen balance and body weight changes. Except for Days 3 and 7, the caloric intake furnished by oral parenteral routes was about 3000 kcal. per day during the first 10 days of TPA therapy; the average daily caloric intake during the 35 day period was 4137. The average daily nitrogen intake was 15.3 Gm. with a net nitrogen loss of 15.8 Gm./day during the first 10 days. The weight loss during this period was very rapid with an average of 1.7 Kg./day. From Days 11 to 35, the body weight was maintained between 73–77 Kg. The average daily nitrogen and caloric intake was 16.5 Gm. and 4684 kcal., respectively, with an average net nitrogen loss of 3.4 Gm./day. Further weight loss was observed when TPA was discontinued and oral intake was inadequate (Fig. 5).

Figure 6 illustrates the fluid, sodium and potassium balance and magnesium intake. It may be noted that the fluid balance which represents intake versus urinary output was always positive. Sodium and potassium retention was observed generally. The average daily caloric intake and fluid, nitrogen, sodium and potassium balances are shown in Table 4. In general, serum electrolytes were maintained fairly constant except for a brief period of slightly decreased sodium and chloride. Plasma glucose was elevated occasionally. Plasma osmolality was maintained fairly normal. Serum urea was not changed (Table 5).

His burn was managed with Sulfamylon initially, followed by debridement in stages and covering of the granulating areas with porcine skin xenografts and skin autografts to the areas of full thickness loss with good results. He was discharged on July 31, 1971 and has continued on outpatient therapy for his residual flexion contractures.

This patient represents a fairly typical major burn. Such patients have an astounding catabolic drain. Despite the attempts made to institute a program for vigorous nutritional supplementation by all routes available, he still lost a total of 16 Kg. during the 35-day period on total parenteral nutrition. This was, in part, due to the difficulties encountered in administering enough nitrogen and calories to meet the extensive loss. The nitrogen loss during the first 6 days on TPA was from 30-35 Gm./day. Beginning from the 8th day of TPA, the nitrogen balance was almost maintained and body weight was stabilized. Nutritional supplementation in the range of 4000 to 6000 kcal./day with a nitrogen intake of 20 to 30 Gm. as amino acids is necessary to maintain a patient with a severe burn in nutritional balance after the initial 10–14 days.

Case 4. H. O. A 70-year-old man was admitted to Vanderbilt University Hospital on April 7, 1970. In 1964 he had undergone

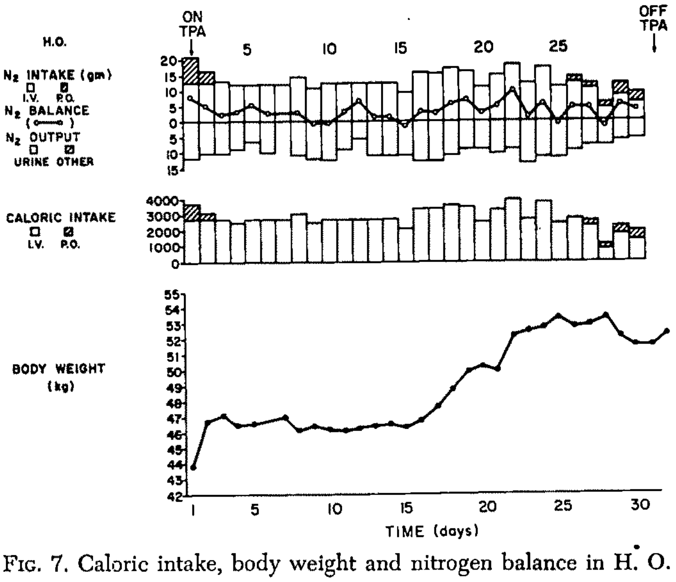


FIG. 7. Caloric intake, body weight and nitrogen balance in H. O.

otal gastrectomy with *en bloc* resection of omentum, spleen, eft hemidiaphragm, left lower lobe of the left lung, body and ail of the pancreas, left lobe of the liver, left adrenal gland nd splenic flexure of the colon. The pathologic diagnosis was eticulum cell carcinoma of the stomach. A Hunt-Lawrence ouch was constructed as a substitute gastric reservoir.[21] His preperative weight was about 70 Kg., but was subsequenty stabilized at around 55 Kg. He had persistent anemia and hypoalbuminemia. During the previous 2 to 3 years, he had begun to ose weight gradually and weighed only 45 Kg. on admission. There was no evidence of a recurrent tumor. A course of nutritional supplementation with TPA was elected and continued for 30 days. During the period of parenteral nutrition, his average daily caloric intake was 2865 kcal. with an average daily nitrogen intake of 13.43 Gm. as crystaline amino acids. The average daily nitrogen retention was 3.32 Gm. and he gained 9.6 Kg. of body weight in a month; most of the weight gain occurred during the second half of the parenteral nutrition period. The changes in body weight, caloric intake and nitrogen balance are shown in Figure 7. He required diuretic therapy for control of pedal edema during this period, but showed no other signs of fluid overload. Figure 8 shows the fluid, sodium, potassium and magnesium balances. As his general conditions improved, he was able to take some food by mouth; TPA was discontinued. He was able to maintain his weight by oral alimentation. One month after discharge from the hospital he weighed 53 Kg. However, his anemia was unchanged and it is of interest to point out that about a year and a half later he developed chronic lymphocytic leukemia.

This patient illustrates the use of TPA as an adjunct to dietary therapy in cases with consistent malnutrition due to chronic illness and to inadequate gastrointestinal function. Patients with marginal adequacy of nutrition may undergo what may be termed as "nutritional decompensation," in which malnutrition and weakness depress their ability to maintain adequate oral intake and a downward spiral is begun. Often, hospitalization and oral nutrition management may suffice to reverse the downward trend. If they do not, TPA should be considered. Once the patient's nutritional state has been restored, he can be expected to maintain that state with oral intake alone.

Discussion

In the past, many patients have succumbed following severe trauma or major surgical procedures simply because of the marked catabolic response imposed upon them; TPA is very useful in such patients. There are other technics available. The use of elemental diets, as advocated by Randall and others,[24] seems valuable in some patients. The intravenous route is necessary in many patients, especially in those undergoing gastrointestinal tract surgery or with intestinal fistulas. The use of TPA is a major undertaking and must be approached with full knowledge of the special technics required and of the hazards which may be incurred. Experience with this technic has shown that it can be carried out safely and with great benefit to the patient if appropriate precautions are taken.

TPA solution containing hypertonic glucose must be delivered into a large central vein. Several methods are available. The use of long polyethylene catheters placed into an arm vein and advanced into the subclavian vein or the superior vena cava has been associated with several difficulties. First, thrombophlebitis often develops around the catheter in the arm after a few days.[1] Second, the polyethylene is stiff and perforation of the great veins or the heart has been encountered. A third hazard, formation of a fibrin sleeve on the indwelling polyethylene catheter, has also been reported.[12]

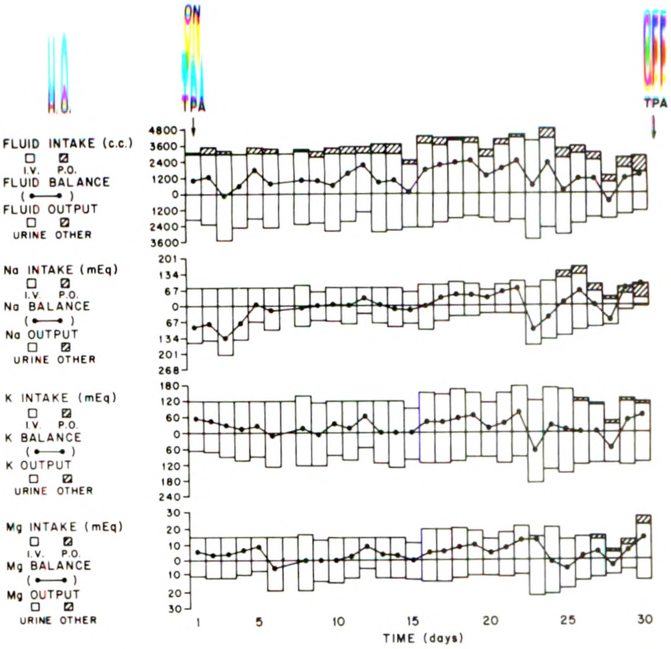


FIG. 8. Fluid, sodium, potassium, and magnesium balance in H. O.

The use of Silastic catheters placed in the external jugular vein through a cutdown and advanced into the subclavian vein or superior vena cava has been fairly satisfactory. Radiographic confirmation of position is necessary. These catheters are minimally reactive and are tolerated for several weeks. Being pliable, they do not perforate the great veins. This is the optimum method in infants. The only drawback is that a cutdown is neces-

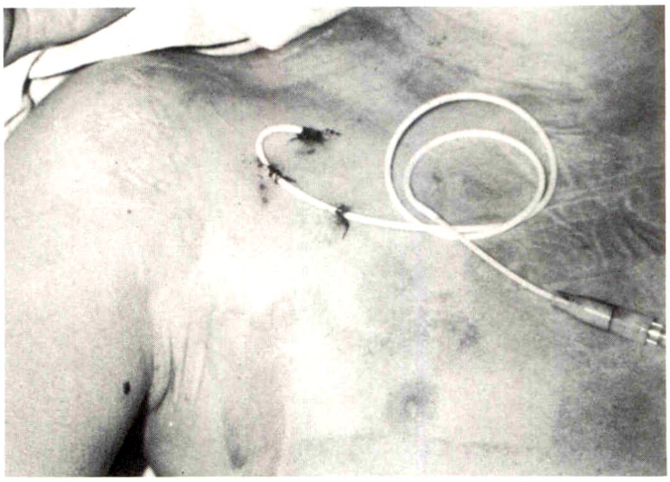


FIG. 9. Silastic catheter placed in right subclavian vein by intraclavicular route for 6 weeks. The catheter was maintained in place by suture fixation to the skin.

sary. Catheters can be introduced through the external jugular vein, [8,10,27] the common facial vein,[28] the internal jugular vein,[5,19] or the cephalic vein.

The use of arteriovenous shunts has been recommended, but we have not used this method.[23] In our experience, the most satisfactory method for long-term total parenteral alimentation has been the placement of a 1.6 mm. Silastic catheter into the subclavian vein percutaneously using the technic described by Wilmore and Dudrick.[8,27] Figure 9 shows a Silastic catheter which had been in position for 4 weeks. Polyethylene catheters have also been placed by this route, with good results. It may be emphasized that placement of the catheter is subject to the usual risks of subclavian venipuncture. It also presents the hazard of cutting the catheter off in the vein during manipulation through the large needle.

Meticulous care must be taken to prevent infections of the catheter and its site of entry. Every 24 to 48 hours the catheter entry site should be cleaned, an antibacterial and antifungal ointment applied to it and a sterile occlusive dressing applied. This should be carried out by a physician or a specially trained nurse.

The problem of sepsis complicating TPA has been emphasized in literature pertaining to parenteral nutrition.[4,6] With the use of technics such as those outlined above in preparing and delivering TPA solutions, delivery should not be a problem. The use of an in-line filter and of an infusion pump seem to be effective in preventing possible infection and in regulating the delivery rate, respectively.

The use of hypertonic glucose may induce hyperglycemia. Patient in normal metabolic balance tolerate infusion of 2700 kcal. per day as glucose without raising the serum glucose over 250 mg./100 ml. Debilitated, elderly, or diabetic patients have often developed hyperglycemia. This can lead to glycosuria and osmotic diuresis, which, if allowed to proceed unchecked, produce the clinical picture of the hyperosmolar syndrome. As water is lost in excess of electrolytes, the patient becomes dehydrated and the serum osmolality rises to over 350 mOsm per liter.

Frequent monitoring of blood and urinary sugar, especially during the early days of infusion of TPA solution, is necessary. It has been our practice to start TPA gradually, working up to three liters of TPA-900 per day in 3 to 4 days. In infants, half-strength TPA-I-900 is begun at a half-strength concentration of 125 ml./Kg/day. The concentration is increased to three-quarter and the full-strength in 4 to 5 days. If hyperglycemia develops, insulin should be administered. Insulin dosage should be based on blood glucose levels. Beginning at 10 units of regular insulin every 4 to 6 hours and progressing upward in steps of 5 to 10 units per dose, has been found to give better control than reliance on a sliding scale of insulin dosage based on the urinary sugar. Because of the great variation of renal threshold for glucose, treatment must be individualized to keep the blood sugar below the level which causes glycosuria in a particular patient. In general, a serum glucose between 100 and 200 mg./100 ml. can be safely maintained and will prevent glycosuria. The rate of infusion of TPA must be maintained fairly constant especially during the period of insulin administration to avoid hypoglycemia due to decreased infusion rate.

The needs for electrolytes vary from patient to patient. TPA solution containing standard amounts may result in deficiency or excess of certain electrolytes. It is suggested that serum electrolytes should be monitored frequently so that the intake may be adjusted. In our experience, the daily intake of 70, 120 and 30 mEq of sodium, potassium and magnesium, respectively has been found satisfactory in most of the patients studied.

It may be pointed out that a solution consisting of crystalline amino acids instead of protein hydrolysate was used as a nitrogen source. It has been reported recently that crystalline amino acids are more completely utilized than protein hydrolysates which contain various amounts of short peptides.[17] Although the present study does not provide evidence with respect to the superiority of crystalline amino acids over protein hydrolysates, amino acid solution seems free of the adverse effects which are occasionally encountered during administration of protein hydrolysate.

The present study confirms our previous report[16] that, in adult patients, total parenteral nutrition furnishing about 12.5 Gm. of nitrogen as crystalline amino acids and 2700 kcal. along with electrolytes and vitamins is capable of achieving positive nitrogen balance, weight gain and promoting wound healing. However, as illustrated by the findings in patient J. H., it would be difficult to provide adequate nitrogen and calorie by total parenteral nutrition alone to overcome the excessive losses in patients with severe burns. Patients with long bone fractures are also known to lose excessive amounts of nitrogen and calories.[14] It may be necessary to supplement total parenteral nutrition with tube feedings of an elemental diet in these patients.

Summary and Conclusion

One hundred and two patients with a variety of pathologic conditions, mostly surgical and traumatic, were given total parenteral alimentation for as long as 62 days with an average of 14 days. The solution consisted of 25% glucose and 0.42 Gm./100 ml. nitrogen as crystalline amino acids along with electrolytes and vitamins which furnished 900 kcal. per liter. The parenteral regimen was delivered into a central vein via an indwelling catheter continuously during the 24-hour period. Results obtained from four patients; one had undergone major operation, one had a severe burn, one had repeated operations, and one had nutritional failure, are presented to illustrate some relevant aspects of parenteral alimentation. It is concluded that except in patients with severe burns, 12.5 Gm. of nitrogen as crystalline amino acids and 2700 kcal. per day along with electrolytes and vitamins is capable of achieving positive nitrogen balance and weight gain, and of promoting wound healing in most of the adult patients studied. In some instances, parenteral alimentation is lifesaving. The procedure is reasonably safe. However, meticulous care must be taken to avoid infection of the central venous catheter and its entry site. Infusion rate must be maintained fairly constant and serum electrolytes and blood and/or urinary glucose must also be frequently monitored.

Acknowledgment

The authors wish to thank Dr. H. William Scott, Jr., for allowing them to include his cases, M.P. and H.O., in this communication, and to McGaw Laboratories for making available the crystalline amino acid preparation, FreAmine® used in our TPA infusate. The enthusiastic secretarial help and painstaking efforts of Mrs. Candy Capers in maintaining patient's records, the technical assistance of Miss Carolyn Pulley, B.S., the clinical assistance of Miss Wanda Wilson, R.N., and the dietary assistance of Miss Gloria Watson, R.D., are also greatly appreciated.

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Depression of Free Water Clearance durin
Pneumococcal Bacteremi

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ACUTE PNEUMOCOCCAL PNEUMONIA is often associated with fluid retention, followed by diuresis occurring after the lysis of fever.[10,21,25] The depression of urine volume during the early phase of a variety of febrile infectious illnesses followed by a postfebrile diuresis was elegantly described by Garratt in 1900.[8] Plasma and extracellular volume spaces have been reported as increased in Rocky Mountain spotted fever[11] and malaria.[5] Studies performed in volunteers with sandfly fever, tularemia and Q fever strongly suggest fluid retention, with depressed urine volume in the early stages followed by an impressive postfebrile diuresis.[3]

The mechanisms by which fluid retention occurs remains unclear. Lathem[17] described a depressed urine volume during the first 2 hours after inoculation of human subjects with typhoid vaccine, which could not be attributed to changes of glomerular filtration rate (GFR). However, few prospective data are available to define the early renal responses which follow the inoculation of animals or man with virulent living microorganisms.[13]

Herein is the reported development of a conscious monkey model which is adaptable to the study of certain renal functions, with acute infection imposed as an experimental variable. The present study documents sequential early physiological renal responses of the rhesus monkey to acute infection with *Diplococcus pneumoniae*, an organism not known to produce a toxin or generally to invade renal tissues. Comparable studies were conducted in control monkeys to define more clearly the types of urine volume changes.

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Materials and Methods

1. *Animal Model.* Seventeen rhesus monkeys (*Macac mulatta*) weighing 2.5 to 3.4 Kg. were maintained o Purina monkey chow and found to be free of infectiou disease for approximately 6 months prior to experimenta tion. All monkeys were studied in the conscious state restrained in metabolic chairs. Two to four days prio to study the monkeys underwent operation, accomplished in approximately 2 hours. Anesthesia during operation was maintained with intermittent 0.2 ml. dose of 2.5% sodium thiomylal through a scalp vein needle i the saphenous vein. The operative procedure in eac monkey was performed under sterile technic with minimal blood loss. Polyethylene catheters (PE-160) wer inserted into both ureters at the bifurcation of the common iliac vessels through a midline lower abdomina incision. The tip of each multiholed catheter was positioned in the renal pelvis, and the external ends wer pulled through separate abdominal stab wounds, abov and lateral to the line of incision. The tip of the exteriorized ureteral catheter was placed in sterile glas containers, thus maintaining a closed system of urin collection. Through a separate incision in the right groin a polyethylene catheter (PE-100) was placed in th femoral vein for infusion of 0.45% saline, paraaminohippurate (PAH) and inulin. In addition, a teflon cathete (internal diameter 0.042 in.) was inserted via the righ femoral artery to a point in the abdominal aorta immediately distal to the renal arteries for the measurement of mean arterial blood pressure (MABP) and fo withdrawal of blood samples. MABP was continuousl monitored during each experiment with a Statham pres

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sure transducer (Statham Instruments, Inc., Oxnard, Calif., Model P23Db). Both femoral venous and arterial catheters were tunneled beneath the skin, exteriorized through a stab wound in the posterior midline adjacent to the first lumbar vertebra, and flushed daily with a heparinized saline solution (50 units of heparin/ml. of saline). No significant problems were subsequently encountered in maintaining patent or sterile ureteral, arterial, or venous catheters. A thermocouple was placed deep in the paraspinal muscles, its tip just external to the retroperitoneum and connected to a 6-channel recorder* for continuous monitoring of body temperatures. Upon completion of operation and recovery from anesthesia, the monkeys were placed in specially constructed metabolic chairs, to which the monkeys became well adapted within 24 hours.

Studies were begun in all monkeys within 2–4 days after operation. Twelve monkeys were expanded to 5% of body weight by i.v. administration of 0.45% saline and maintained at or slightly above this level by replacing urinary loss plus an additional 5% of the urinary loss. Upon the initiation of volume expansion, a separate sustaining infusion of 0.45% saline containing PAH and insulin was administered via the femoral vein catheter after appropriate loading doses, calculated to maintain the plasma PAH and inulin levels at 1-2 and 15-25 mg./100 ml. respectively throughout the entire experimental period. A 90-minute equilibration period followed the completion of volume expansion in each monkey. After equilibration, 2 hours of baseline collections were obtained in each monkey prior to actual or sham inoculation.

2. *Experimental Design*

Group I (*Control Monkeys*). This group consisted of six monkeys which were sham-inoculated i.v. with 1 ml. of normal saline at zero time. This group served to determine renal function in the conscious monkey over an 11-hr period, following the initiation of volume expansion.

Group II (Early Bacteremia). This group consisted of six monkeys which were inoculated i.v. at zero time with 1–5 × 10^8 virulent *D. pneumoniae,* Type Ia, suspended in 2 ml. of sterile saline. Bacterial counts of the inoculum were verified by serial dilution and culture plate analysis. Concurrent studies demonstrated that 20 monkeys inoculated with the same quantity of Type Ia pneumococci had positive blood cultures at 24 hours (personal communication, Dr. Robert H. Fiser, USAMRIID). Experiments in Groups I and II were accomplished on alternate days. Five additional bacteremic monkeys were studied at a later date (see results).

3. *Sample Collections and Clearances*

After completion of the equilibration period of each monkey, urine was collected every 20 minutes for 11 hrs; the first 2-hr collection (hr −2 and −1) constituted the baseline collections used to determine control values for individual monkeys. The experimental variable was introduced at zero time, the end of the second hour of baseline observations. Blood was withdrawn for all plasma and serum measurements at the midpoint of each hour, and estimated values used for calculating each 20 minute clearance period were extrapolated from the midhour data. Urine from both kidneys was pooled and an aliquot from each 20 minute period was frozen for later chemical determinations. Clearances of inulin (C_{in}), PAH (C_{PAH}), urea (C_{urea}), osmolar (C_{osm}) and free water (C_{H_2O}) were calculated from standard formulae. Urinary volume (V), C_{H_2O} and C_{osm} were expressed as ml./min and ml./min/100 ml. of GFR and Na excretion ($U_{na}V$) as mEq/hr and mEq/hr/100 ml. GFR. Other measurements include percent Na reabsorption and K excretion.

4. *Chemical Determination*

Blood samples from the arterial catheter were withdrawn into heparinized syringes for measurement of inulin, PAH, plasma urea nitrogen (PUN), hematocrit, white blood cell (WBC) count and osmolality. The red cells were separated from the plasma under sterile conditions and returned to the animal in an equal volume of saline within 15 min. Clotted blood was used for serum Na and K determinations. Blood sampling never exceeded 6 ml./hr of whole blood. Plasma and serum were also frozen for later chemical determinations. Inulin and PAH were measured in a Technicon* autoanalyzer using a modification of the technic of Dawborn and Harvey.[7,12] Na and K were analyzed by standard flame photometry, and osmolality with a wide range osmometer.†

Results

Volume expansion with hypotonic saline has the advantage of facilitating recognition of changes in C_{H_2O} but the disadvantage of masking subtle changes in $U_{na}V$. The results reported herein were accomplished under relatively constant conditions of volume expansion (5% of body weight) in order to interpret more clearly group differences in free water clearance.

Group I (Control)

Prior data detailing renal function in the conscious monkey under conditions of hypotonic saline volume

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* Minneapolis-Honeywell, Brown Instruments, Philadelphia, Pa., Model Y153X60.

* Technicon Corp., Rochester, N.Y.

† Advanced Instruments, Inc., Newton Highlands, Mass.

TABLE 1. *Renal Function During Volume Expansion Control (Group I) vs Infected (Group II)*

PARAMETERS†	GROUP	HOURS										
		-2	-1	1	2	3	4	5	6	7	8	9
C_{in}	I	13.0±2.8	9.5±1.0	9.6±0.8	10.0±1.3	10.7±1.0	9.6±1.1	10.2±0.9	9.1±0.6	7.8±0.8	9.0±1.2	10.3±1.1
ml/min	II	10.0±1.4	10.4±2.0	10.4±1.5	10.0±1.2	9.4±1.5	9.1±0.6	8.1±0.6	8.1±0.9	8.8±1.7	9.6±2.6	9.8±2.3
C_{PAH}	I	76.4±14.4	56.1±7.3	49.7±6.4	59.3±14.3	66.1±12.4	44.1±8.2	58.7±8.8	54.1±7.5	43.6±4.7	47.3±7.2	53.9±10.0
ml/min	II	44.6± 4.7	50.0±9.6	49.4±4.8	38.8± 4.4	50.3± 9.0	50.9±5.4	45.4±4.4	51.0±9.1	51.7±8.0	46.9±7.0	59.2± 1.2
F F	I	0.19±0.03	0.18±0.01	0.21±0.03	0.20±0.03	0.18±0.02	0.25±0.03	0.19±0.02	0.18±0.02	0.19±0.02	0.20±0.02	0.22±0.04
	II	0.22±0.03	0.22±0.03	0.22±0.02	0.28±0.04	0.20±0.04	0.18±0.01	0.19±0.01	0.18±0.02	0.17±0.02	0.20±0.04	0.18±0.03
C_{urea}	I	11.1±5.1	16.0±9.4	14.7±8.4	7.2±1.0	7.8±0.8	7.9±1.9	13.3±6.8	10.5±4.9	11.6±5.8	12.6±7.1	12.6±7.6
ml/min	II	6.7±1.1	6.4±1.3	6.1±0.9	6.7±1.2	5.7±1.3	4.3±0.7	4.3±0.7	4.2±1.1	4.9±1.6	4.9±1.6	4.4±1.1
V	I	13.3±3.0	17.1±4.3	15.6±4.9	15.1±5.0	17.0±6.4	19.3±7.4	16.1±5.1	18.6±6.9	22.3±10.5	18.1±6.5	13.7±5.3
ml/min/100ml GFR	II	12.4±1.7	11.3±2.1	9.2±2.0	7.6±1.2	7.6±1.8	5.9±1.2*	5.8±1.2*	5.2±1.8*	5.1±1.3*	5.6±1.2*	6.5±1.2*
V	I	1.3±0.2	1.3±0.2	1.4±0.3	1.4±0.4	1.6±0.5	1.4±0.4	1.5±0.3	1.4±0.4	1.4±0.4	1.5±0.5	1.6±0.5
ml/min	II	1.2±0.2	1.1±0.2	0.9±0.2	0.7±0.2	0.7± 0.2	0.6±0.1*	0.5±0.3*	0.3±0.0*	0.3±0.1*	0.5±0.2*	0.6±0.2*
C_{osm}	I	5.1±1.6	7.8±2.9	7.9±3.3	8.2±2.3	8.7±2.2	11.0±2.9	10.1±2.8	9.7±2.3	12.4±3.4	10.9±1.8	8.5±2.5
ml/min/100 ml GFR	II	5.3±1.4	5.4±1.4	5.7±1.3	6.3±0.7	7.1±0.8	4.9±0.3	4.8±0.6	4.7±0.6	5.1±0.6	5.3±1.0	5.2±0.6
C_{H_2O}	I	8.2±2.6	9.4±2.2	7.7±2.5	6.8±3.6	8.3±4.8	8.3±4.6	6.0±2.4	8.9±4.6	10.0±7.2	7.2±4.8	5.2±2.8
ml/min/100ml GFR	II	7.1±0.9	5.9±1.7	4.4±1.3	1.2±0.6*	0.5±1.2*	1.0±1.3*	1.0±0.9*	0.5±1.4*	0.1±0.9*	0.3±1.0*	1.3±1.1*
U/P_{osm}	I	0.5±0.1	0.5±0.1	0.5±0.1	0.7±0.1	0.8±0.2	0.8±0.2	0.7± 0.1	0.7± 0.1	0.7±0.1	0.8±0.1	0.7±0.1
	II	0.4±0.1	0.5±0.1	0.6±0.1	0.9± 0.1	1.1±0.1	0.9±0.1	0.9±0.1	1.1±0.1	1.1±0.1	1.1±0.2	1.0±0.2
$U_{na}V$	I	11.3±4.1	20.2±9.1	20.6±10.2	21.0±7.1	23.2±7.9	30.3±11.2	27.4±9.6	24.5±8.4	33.5±13.4	29.7±7.6	22.4±8.1
mEq/hr/100 ml GFR	II	10.0±4.2	11.1±4.2	12.1±4.1	13.9±2.9	13.6±2.2	9.7±6.8	9.0±1.3	8.2±1.3	7.8±0.4	7.0±1.0	8.1± 1.5
% Na	I	96.2±1.4	93.3±3.1	93.2±3.5	91.8±2.7	92.2±2.8	90.0±3.8	91.1±3.3	95.1±1.1	88.4±4.7	90.8±2.3	91.6±2.5
reabsorbed‡	II	96.4±1.4	96.3±1.4	96.0±1.5	95.5±1.0	95.8±0.7	96.9±0.3	97.0±0.4	97.6±0.4	97.3±0.3	97.4±0.3	97.3±0.5
U_KV	I	0.6±0.1	0.7±0.1	0.6±0.1	0.7±0.1	0.7±0.1	0.8±0.1	0.8±0.1	0.6±0.1	0.5±0.1	0.6±0.1	0.6± 0.0
mEq/hr	II	0.7±0.1	0.6±0.1	0.6±0.1	0.7±0.1	0.8±0.2	0.7±0.1	0.6±0.1	0.5±0.1	0.6±0.1	0.5±0.0	0.5±0.0
Na (Serum)	I	151±1.6	154± 2.4	158±4.3	154±4.8	156±4.0	157±4.4	158±2.8	158±2.6	158±5.5	163±3.4	155±4.9
mEq/liter	II	148±2.2	154± 2.9	158±7.6	156±4.4	161±2.4	157±3.8	159±4.1	159±4.7	164±3.5	158±3.4	154±2.9
K (Serum)	I	3.8±0.1	3.8± 0.1	4.0±0.2	3.9±0.1	4.2±0.2	4.0±0.2	4.1±0.2	3.7±0.2	4.0±0.3	4.5±0.3	3.8±0.2
mEq/liter	II	3.8±0.4	3.8±0.2	4.0±0.1	4.2±0.4	3.7±0.2	3.6±0.2	3.8±0.3	4.1±0.3	4.1±0.2	4.3±0.3	3.9±0.2
Osm (Plasma)	I	308±4.0	316±5.7	318±6.7	316±7.5	317±6.6	320±6.5	314±6.2	314±6.1	312±7.5	316±8.1	306±7.8
mOsm/liter	II	308±3.1	311±3.4	314±1.6	327±3.8	317±3.8	318±3.1	314±3.4	325±3.7	320±5.1	314±3.9	310±3.5
Urea (Plasma)	I	17.2±1.5	15.2±1.7	15.0±1.5	14.4±1.5	14.2±1.6	15.3±1.1	15.8±1.4	16.9±1.4	16.4±1.5	17.6±2.7	16.3±2.0
mg %	II	19.1±4.0	17.8±4.1	17.6±3.9	16.9±4.0	17.2±4.2	17.2±4.1	17.8±4.0	18.2±3.9	19.0±3.8	18.9±4.0	19.6±3.9

*REPRESENTS p VALUE OF AT LEAST 0.01 OR LESS USING THE PAIRED "T" TEST

†ALL MEASUREMENTS REPRESENT MEAN HOURLY GROUP VALUES ±SE

‡CALCULATED FROM THE FORMULA $\frac{\text{Na FILTERED-Na EXCRETED}}{\text{Na FILTERED}}$ X 100 WHERE Na FILTERED = $\frac{\text{SERUM Na X GFR X 60}}{1000}$ AND

Na EXCRETED = mEq/hr

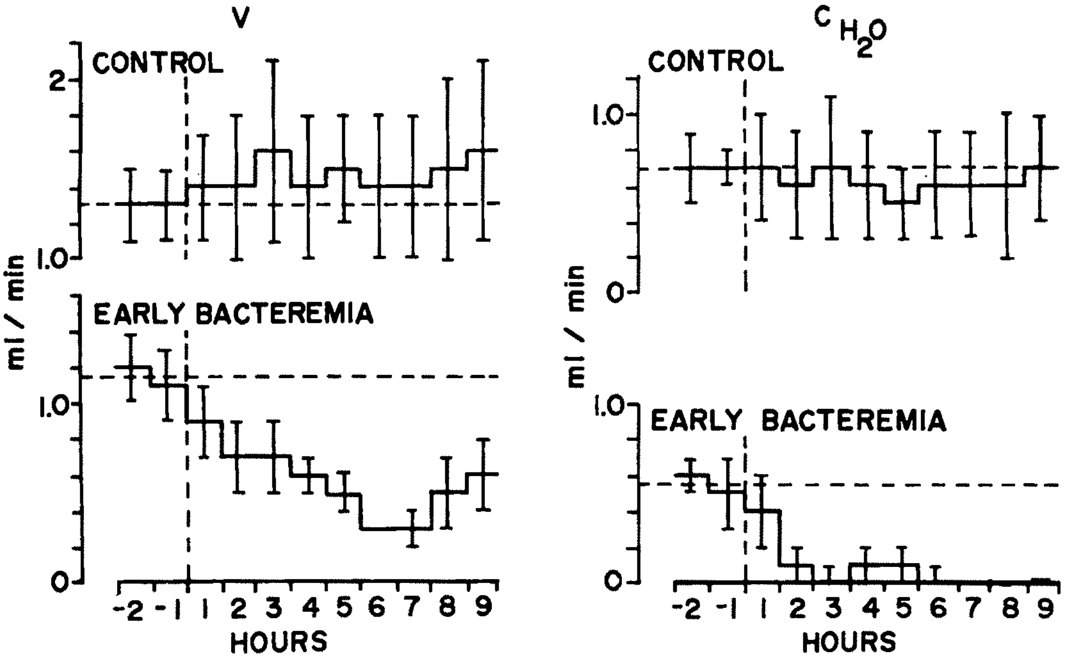

FIG. 1. Depicts the decline of V and C_{H_2O} ($p < 0.001$) in Group II monkeys inoculated with *D. pneumoniae* at zero time. Relatively stable values are apparent in Group I controls.

expansion have not been reported. Our control monkeys accomplished this objective and also served as a baseline from which to evaluate changes in renal function which occurred after pneumococcal inoculation. Control monkeys excreted an average urine volume of 1.44 ml./min over an 11-hr period. Since urine volume (plus 5% of urine volume) was replaced with 0.45% saline i.v., the maintenance of 5% body weight expansion required an infusion of hypotonic saline averaging 997 ml. administered over 11 hr. Although monkey weights were not obtained at the conclusion of each experiment, this represents approximately 33% of body weight in a 3 Kg. monkey and demonstrates an enormous capability of the conscious rhesus monkey to accommodate and readily excrete large amounts of hypotonic saline. However, this also represents a considerable Na load resulting in a rise in serum Na and plasma osmolality up to hr +4 (Table 1), demonstrating the monkey's initial ability to more readily excrete water than Na. Hours +5 and +9 show the plasma osmolality returning toward baseline levels. Similar responses of serum osmolality and urine Na and water excretion to volume expansion have been previously described.[27,29]

The mean hematocrit and WBC obtained during baseline collections was 30% and 6,200/mm^3 respectively and remained at or near this level during the entire experimental period. PUN ranged between 14.2 and 17.6 mg./100 ml., with no significant trends.

Average body temperature ranged from 99.3 to 102.2 F. The rise of temperature in Group I (Fig. 2) slightly exceeds the normal 2° midafternoon diurnal temperature elevation but clinical illness was not apparent; WBC was normal; the urine cultures were sterile. The average range of MABP was 103-114 mm. Hg; no individual monkey declined below a MABP of 80 mm. Hg.

GFR as measured by C_{in} showed a mean baseline value of 11.3 ml./min; a slight decline occurred over the 11 hr (Table 1). Effective renal plasma flow (RPF) as measured by C_{PAH} showed a mean baseline value of 66 ml./min and demonstrated a mild but significant decline ($p < 0.05$) by the seventh hour postinoculation (Table 1). Filtration fraction (FF) averaged 0.18 during baseline hours with most values ranging between 0.18 and 0.22 (Table 1). Similar values of C_{in}, C_{PAH} and FF have been previously described in our laboratory (14). C_{urea} did not deviate significantly from the mean baseline value of 13.5 ml./min (Table 1).

Urine Na excretion increased from a mean baseline value of 3.9 to 7.4 mEq/hr in hr +9 (Fig. 3) and mean values corrected for GFR are depicted in Table 1. The rise in $U_{na}V$ attained statistical significance at hr +5 and +8 (Fig. 3) and the amount of actual Na excreted was equivalent to 89% of the Na administered from hr −2 to +9. Serum Na and plasma osmolality increased significantly ($p < 0.05$) from baseline values and serum K and urine K excretion ($U_K V$) remained relatively stable (Table 1).

Urine volume (V) increased from a mean baseline value of 1.3 to 1.6 ml./min in hr +9 and C_{H_2O} remained stable between 0.5 and 0.7 ml./min with no statistically significant changes in either parameter (Fig. 1). The increase in V is due primarily to the rise in C_{osm} which is significantly increased ($p < 0.05$) from 0.6 to 0.9 ml./min (Fig. 3). Identical trends of excretion are seen in Table 1, where C_{H_2O} and C_{osm} are corrected for GFR. The rise of C_{osm} was accompanied by a significant in-

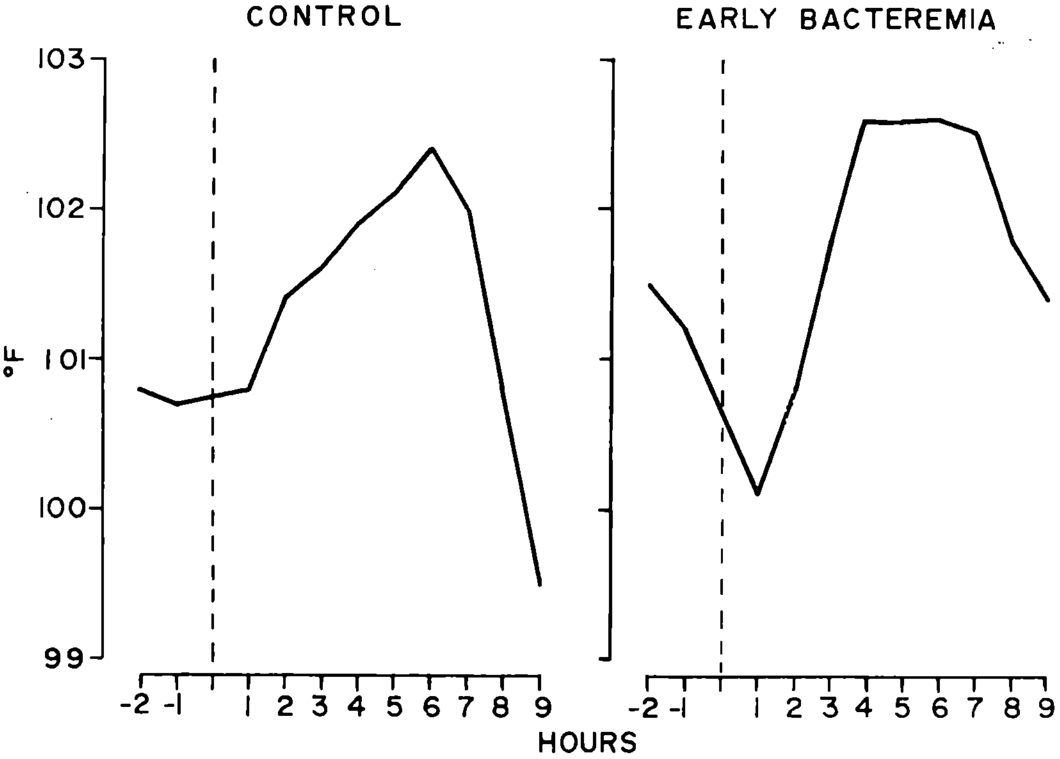

FIG. 2. Temperatur curves of control an early bacteremic mon keys. Curves are derive from mean group value recorded at half-hourl intervals.

crease ($p < 0.05$) of the hourly urine/plasma osmolar ratios over baseline values which occurred in parallel with the rise in $U_{na}V$ (Table 1).

Group II (Early Bacteremia)

Measurements of hematocrit, PUN, MABP and temperature were in the same range as control monkeys with no significant differences. In contrast to control monkeys, early bacteremic monkeys showed mild leukopenia and an increased percentage of polymorphonuclear leukocytes. In addition, the decline of temperature after hr +6 is less than that of control monkeys (Fig. 2).

Early bacteremic monkeys demonstrated a decline in C_{in} which was not significantly different from control monkeys (Table 1), with a mean baseline C_{in} of 10.2 ml./min. In contrast to the significant decline seen in control monkeys, effective RPF showed a slight rise in early bacteremic monkeys (Table 1).

Urine Na excretion showed a gradual increase from a mean baseline value of 3.3 to 4.3 mEq/hr by hr +2 and declined to below baseline values for the duration of the study. After inoculation, $U_{na}V$ was notably less than control monkeys (Table 1 and Fig. 3) in that early bacteremia monkeys received approximately half the amount of total Na load administered to control monkeys because of their depressed urine V. Even so, early bacteremia monkeys excreted 96% of the administered Na load while control monkeys excreted 89%. Similar to control monkeys, serum Na and osmolality rose significantly, and serum K and U_KV remained essentially unchanged.

The most interesting changes involved V and C_{H_2} which showed a rapid and dramatic decline after pneumococcal inoculation. Urine V declined from a mea baseline value of 1.2 to 0.3 and C_{H_2O} from 0.6 to 0. ml./min (Fig. 1). Mean free water clearance did no become negative during any averaged hour, although negative C_{H_2O} was occasionally seen in individual monkeys in Group II. The U/P osmolar ratio rose, thi change being more significantly elevated above baselin values in Group II ($p < .001$) than in Group I ($p < 0.05$). U/P ratios slightly above 1.0 occurred simultaneously, with minimally positive free water clearances i hours +6 and +7. This was accounted for by grou averaging. The rapid and highly significant ($p < 0.001$ decline in V and C_{H_2O} seen in early bacteremia monkey was in sharp contrast to the stable values seen in control monkeys (Fig. 1). In that C_{osm} does not change significantly in bacteremic monkeys, the decline in V i mainly due to the depressed C_{H_2O}. Corrected values of V C_{H_2O} and C_{osm} are depicted in Table 1.

The above data did not completely establish that th depression of C_{H_2O} was related to infection for it wa conceivable that the lower infusion rate of hypotoni saline in bacteremic monkeys was responsible for a lowe C_{H_2O}. Accordingly, we elected to study five additiona bacteremic monkeys using the same experimental protocol, but changing the rate of 0.45% saline infusion to equal the rate of urine excretion in Group I monkeys (Table 2).

Temperature rose from an average baseline value of 100.7 to a peak of 101.5 at hr +4. Pneumococcal bacteremia was documented in all monkeys at the end of each experiment. MABP was comparable to both previous groups.

As illustrated in Table 2, there is an early marked depression of C_{H_2O} by hr +2, with 3 of 5 monkeys in negative free water clearance. This was not secondary to decreased sodium delivery to the ascending loop of Henle in that $U_{na}V$ was increased over baseline values. In addition, 948 ml. of hypotonic saline was administered i.v. to each monkey, resulting in an average total urine volume excretion of 644 ml. (range 504 to 730 ml.; SE 34) from hours −2 through +9. Consequently, all monkeys attained a body weight expansion greater than ten percent! This degree of expansion significantly increased C_{osm} ($p < 0.025$ during hr +6 to 9) and $U_{na}V$ ($p < 0.01$ during hr +2 to 7) as expected. The direction and magnitude of serum Na and osmolality changes were comparable to Groups I and II.

Discussion

Changes in renal function are known to follow the experimental administration of bacterial toxins[20,22] but such toxins do not necessarily simulate the overall effects of a generalized infection. Renal function may be ininfluenced during the course of a generalized infectious illness by the presence of fever[4,9,14,15] and altered cardiovascular,[16] endocrine,[1,2,6,19] acid-base,[23] water, electrolyte, mineral and nitrogen equilibria,[3,6,10,25] as well as by complicating phenomena such as shock.[24,26] In the present study, renal functions were monitored before and after inoculation with infectious organisms. Changes were compared to baseline measurements from the same monkeys and also to data obtained in control monkeys studied under identical experimental conditions.

Serial values of GFR and effective RPF obtained in early bacteremic monkeys were not significantly different from control monkeys. Renal hemodynamic changes in both groups of monkeys could not be attributed to fluctuations in MABP or to fever. Although extraction ratios of PAH were not obtained, previous studies with i.v. inoculation of heat killed typhoid organisms failed to show decreased PAH extraction.[18]

Hypotonic saline was elected as the means of inducing a free water diuresis and we have attempted to define the response of rhesus monkeys to 5% expansion of body weight with hypotonic saline. In control monkeys, an increase occurred in V, C_{osm} and $U_{na}V$ above baseline values and C_{H_2O} showed a slight decline. Urine Na excretion and C_{osm} showed a significant parallel increase, the latter accounting for the rise in V. The rise in serum Na and plasma osmolality attests to the monkeys ability to excrete water more readily than Na, and in this respect, is similar to man.[27] Despite a rising plasma osmolality, C_{H_2O} remains distinctly positive in all monkeys. This constitutes indirect evidence that volume expansion, controlled at 5% of body weight, may particularly suppress antidiuresis in our monkey model, despite a rising plasma osmolality. This phenomenon is indirectly supported in recent studies by Zehr et al. in the unanesthetized ewe.[30] These investigators demonstrated suppression of plasma antidiuretic hormone (ADH) levels with elevated left arterial pressure, the suppression being most marked when the increase in plasma osmolality was restricted to 2 to 3% of control values.

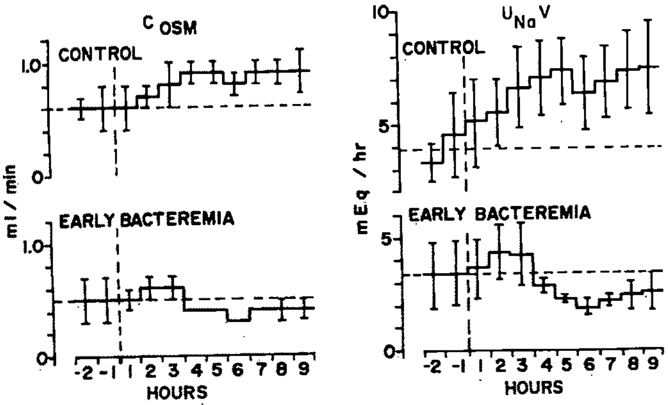

FIG. 3. C_{osm} and $U_{na}V$ demonstrate opposite trends after hr +3, resulting from differences in sodium load. The rise of $U_{na}V$ and C_{osm} in Group I controls is significant ($p < 0.05$) during hr +5 and +8.

Little is known about the renal handling of salt and water during initial stages of an infection. Prospective studies in human volunteers inoculated with tularemia, sandfly fever and Q fever suggested that an initial saliuresis preceded by one day the onset of fever.[3] Shortly thereafter occurred the well documented period of renal salt and water retention characteristic of certain acute febrile illnesses. Following lysis of fever, recovery from illness was typically followed by a brief period of diuresis. Water retention from possible inappropriate ADH secretion has also been associated with numerous infections.[1]

The phenomenon of low urine volume and depressed chloride excretion associated with the early stages of febrile illnesses was described in the early part of this century.[8] Pneumococcal infection in man, particularly lobar pneumonia,[21,25] is often associated with water retention. Subsequent reports also document the occurrence of a brisk diuresis which follows lysis of infectious fevers.[3,10]

Similar to pneumococcal pneumonia in humans, inoculation of pneumococcal organisms in volume expanded Group II rhesus monkeys produced marked fluid reten-

TABLE 2. *Fluid Retention During Pneumococcal Bacteremia*

PARAMETERS+ GROUP	HOURS -2	-1	1	2	3	4	5	6	7	8	9
C_{in} ml/min	17.7±3.6	13.0±2.4	11.4±1.1	13.3±2.1	14.0±2.7	12.6±2.5	12.2±2.0	12.0±3.0	11.8±2.8	11.7±2.8	9.0±2.2
C_{PAH} ml/min	112.4±27.2	71.4±11.7	61.9±7.8	78.9±17.2	78.3±16.6	74.7±22.2	86.1±12.5	86.1±17.4	70.7±13.8	82.9±18.4	53.1±13.6
FF	0.17±0.01	0.18±0.01	0.19±0.01	0.17±0.01	0.19±0.03	0.18±0.03	0.13±0.01	0.13±0.01	0.17±0.02	0.14±0.02	0.14±0.02
V ml/min/100 ml GFR	6.3±2.4	8.4±2.1	7.0±2.6	6.1±2.3	10.1±1.8	12.2±3.2	9.8±2.8	10.6±1.9	10.8±3.0	8.7±2.9	12.7±3.2
V ml/min	0.72±0.2	0.90±0.1	0.73±0.2	0.67±0.2	1.26±0.1	1.29±0.2	1.01±0.1	1.08±0.1	1.07±0.2	0.93±0.3	1.09±0.3
Cosm ml/min/100 ml GFR	3.6±1.0	3.8±1.3	4.4±2.0	6.2±1.9	6.4±1.6	6.8±2.3	6.8±2.5	7.8±1.9	8.5±2.0	7.6±1.7	8.7±1.8
C_{H_2O} ml/min/100 ml GFR	2.7± 1.3	4.6±0.9	2.7±1.0	-0.1±0.5*	3.7±1.2	5.4±1.6	3.0±1.0	2.8±0.5	2.3±1.2	1.1±1.4	4.0±1.4
U/P_{osm}	0.8±0.2	0.4±0.0	0.6±0.2	1.1±0.1*	0.6±0.1	0.6±0.1	0.7±0.1	0.7±0.0	0.8±0.0	1.0±0.1	0.7±0.0
$U_{na}V$ mEq/hr/100 ml GFR	9.8±6.1	14.6±9.9	19.3±14.5	29.8±13.7	35.6±12.6	38.4±17.9	40.1±17.5	44.0±133	45.3±10.6	42.7±11.3	48.6±12.7
% Na reabsorbed‡	98.8±0.7	98.2±1.2	97.7±1.7	96.5±1.6	95.6±1.6	95.5±2.1	95.3±2.1	94.9±1.5	94.6±1.3	94.3±1.4	94.2±1.4
U_KV mEq/hr	0.7±0.1	0.7±0.1	0.5±0.1	0.8±0.1	0.9±0.1	0.7±0.1	0.7±0.1	0.8±0.1	0.9±0.1	0.9±0.1	0.8±0.1
Na (Serum) mEq/liter	139±1.1	139±0.4	141±0.7	139±0.5	139±1.4	142±1.4	145±0.7	145±0.5	142±1.2	143±2.3	136±2.4
K (Serum) mEq/liter	3.5±0.1	3.4±0.1	3.4±0.1	3.4±0.2	3.3±0.1	3.1±0.1	3.2±0.0	3.2±0.0	3.2±0.0	3.2±0.1	3.2±0.2
Osm (Plasma) mOsm/liter	275±6.8	284±6.5	280±5.6	279±7.6	285±9.1	288±8.7	293±6.7	290±9.6	290±4.5	287±4.8	283±3.8
Rate of 0.45% saline infusion - ml/hr	78	78	84	84	96	84	90	84	84	90	96

* REPRESENTS p VALUE OF AT LEAST 0.01 OR LESS USING THE PAIRED "T" TEST

+ ALL MEASUREMENTS REPRESENT MEAN HOURLY GROUP VALUES ±SE

‡ CALCULATED FROM THE FORMULA $\frac{\text{Na FILTERED - Na EXCRETED}}{\text{Na Filtered}}$ X 100 WHERE Na FILTERED = $\frac{\text{SERUM Na X GFR X 60}}{1000}$ AND

Na EXCRETED = mEq/hr

tion. Urine volume rapidly declined and remained significantly depressed ($p < 0.001$) throughout the remainder of the 11 hours of study. A marked decline of C_{H_2O} ($p < 0.001$) coincided with this change. Both C_{osm} and $U_{na}V$ demonstrated a slight initial rise but stabilized near baseline values from hr +4 to +9.

Unlike control monkeys, $U_{na}V$ and C_{osm} did not show a sustained rise in Group II early bacteremic monkeys. This is not surprising in that these bacteremic monkeys, on the basis of urine volume replacement, received slightly less than 50% of the fluid and salt load of control monkeys. Reduced volume replacement is, however, secondary to the primary occurrence of depressed free water clearance. This was clearly demonstrated in the bacteremic monkeys which were infused with hypotonic saline at the same rate as control monkeys. This group (Table 2) yielded important additional data demonstrating that a decreased rate of fluid replacement and/or decreased delivery of sodium to the diluting segment were not responsible for the early depression of C_{H_2O}. In addition, the stimulus of progressive volume expansion could account for the progressively increased $U_{na}V$ in these monkeys, along with the failure of a sustained depression of C_{H_2O}.

Our studies, therefore, demonstrate a marked difference between early bacteremic and control animals in C_{H_2O} via the kidney. The mechanism by which this occurs is not clear. A rise in plasma osmolality due to massive infusion of hypotonic saline occurs in both control and early bacteremia monkeys. Elevation of the plasma osmolality, a potent stimulus for ADH release,[28] cannot by itself account for the sustained depression of C_{H_2O} seen in early bacteremic monkeys since plasma osmolality rose in a similar fashion in control monkeys. Decreased extracellular volume is eliminated as a contributing factor by experimental design. Data has been presented which strongly suggests that the depression of C_{H_2O} in experimental monkeys was independent of changes in GFR. A direct stimulatory effect on the hypothalamic-pituitary axis, resulting in release of ADH, has been attributed to hyperthermia.[14] This mechanism would not apply to our studies in that the temperatures of control and experimental monkeys were fortuitously similar during the period of maximal C_{H_2O} decline. Finally, an increase of medullary tonicity, redistribution of renal blood flow and, a direct effect of infection on release of ADH, are other possible mechanisms which should be considered. Further studies are clearly needed to document the mechanism of water retention during early pneumococcal bacteremia.

Summary

The mechanism of water retention during febrile infectious illnesses is not known. Accordingly, 12 conscious rhesus monkeys were studied for 11 hr 2–4 days after operation. Monkeys were volume expanded to 5% of body weight with 0.45% saline and subsequent urinary losses were replaced. Following 1.5 hr equilibration and 2 hr of baseline collections, six monkeys were inoculated intravenously (i.v.) with 10^8 virulent pneumococci and 6 control monkeys were sham-inoculated with 1.0 ml. of saline. Free water clearance (C_{H_2O}) of control monkeys remained essentially unchanged, averaging 7.8 ml./min/100 ml. glomerular filtration rate (GFR) over 11 hr. Urine osmolality rose and urine volume declined in infected monkeys within 1 hr of inoculation, resulting in a prompt decline of C_{H_2O} from 6.5 to 1.2 by the second hour postinoculation; C_{H_2O} thereafter remained depressed at 1.3 ml./min/100 ml. GFR or less. Decreased C_{H_2O} in infected monkeys could not be related to changes in plasma osmolality, extracellular volume, glomerular filtration or renal plasma flow (RPF) and both groups excreted a like percentage of their sodium loads. Mechanisms possibly related to the antidiuresis of infection are discussed.

Acknowledgment

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Late Results of Successful Replantation of Upper and Lower Extremities

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DURING the last 10 years only a small number of successful replantation of extremities severed by trauma have been reported.[1,6,7,11] The importance of this procedure is not only the immediate success of the operation but above all the late results of the replantation. In our opinion this success depends on the precise and accurate reconstruction of the injured anatomical structures during the first operation. There are still differences in opinion among authors concerning this special operative procedure, the type of neural suture used and the time at which the severed nerve endings are joined.[5,8,10]

Therefore the two patients, in whom we have replanted a leg in one and an arm in the other after amputations by trauma and we have followed 5 and 2 years respectively, may contribute to the solution of this problem. The second patient is of special interest because the amputated arm was lost for a 2-hour period.

Case Reports

Case 1. J. G., a 54-year-old man was admitted to Berlin-Neukölln City Hospital on October 28th 1964, approximately 30 minutes after a train accident in which the right thigh was amputated just above the knee joint. Only a small lateral skin bridge remained intact (Fig. 1). There was also a severe laceration of the left thigh with heavy damage to soft tissue as well as a fracture of the femur. Both wounds were dirty and covered with oil and sand. The wounds were debrided and cleaned with physiological saline solution and penicillin. Circulation was restored 3½ hours after amputation through anastomoses of the popliteal vein and artery. The continuity of both nerves—internal and external popliteal—was reestablished by primary suture. Alignment and stability of the femur was attained by balanced traction. Musculo-fascial layers were repaired with mersilene or catgut and the severely damaged skin was closed.

Postoperative Course

Circulation in the thigh was normal and remained unchanged. Marked edema in the first 2 weeks disappeared completely. Galvanic stimulation of the denervated muscle groups was begun on the 2nd week after injury and was continued daily for more than 1 year. The necrotized area of skin in the knee hollow was replaced by skin autografts during the 6th week. Physic therapy with passive motion of joints was started during the 4th week. An aseptic fistula in the knee hollow caused by a number of sequestered bone chips closed promptly after the extirpation of the bone fragments. The stability of the femur allowed us to remove the extracutaneous fixation and traction after 12 weeks.

Return of Function

The first active motion in the flexor muscle group was observed 14 months after injury. Between the 14th and 20th months there was a complete return of motor and sensory function of the tibial nerve.

Active motions of the flexor muscles and the small plantar muscles and the regaining of partial sensibility permitted free movement and weight bearing on the leg. About 1½ years after the accident the patient could walk without any help (Fig. 2).

Present Status

The patient is currently able to walk and to care for himself. The function of the leg is restrained because the peroneal nerve is still paralyzed. This loss can be partially compensated by orthopedic shoes. All functions of the tibial nerve can be seen. There is no shortening of the leg and no severe dystrophy.

The active movement in the knee joint is 175° extension and 110° flexion. In the foot joint a plantar flexion of 30° is possible but no active dorsal extension. The pronation and abduction of the foot is not possible because of the paralysis of the peroneal nerve. In the region innervated by the fibular nerve there is no sensitivity on the dorsal surface of the foot.

Case 2. R. K., an 8-year-old boy was brought to the University Hospital of Berlin-Westend on the 24th of June 1969, about 40 minutes after falling from a moving train in which case the right arm had been amputated completely above the elbow joint.

There was also a deep tangential wound at the right chest side with fracture of ribs and an open pneumothorax (Fig. 3). Two hours after admission the police succeeded in finding the severed arm near the railroad track and brought it to the hospital. The arm was immediately preserved in ice immersion to lower the

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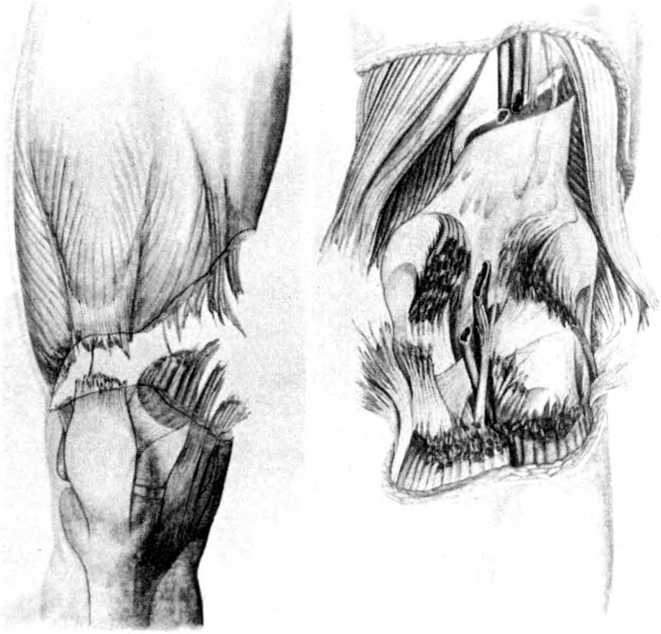

FIG. 1. The drawing shows the nature of the amputation. Only a lateral skin bridge remained intact.

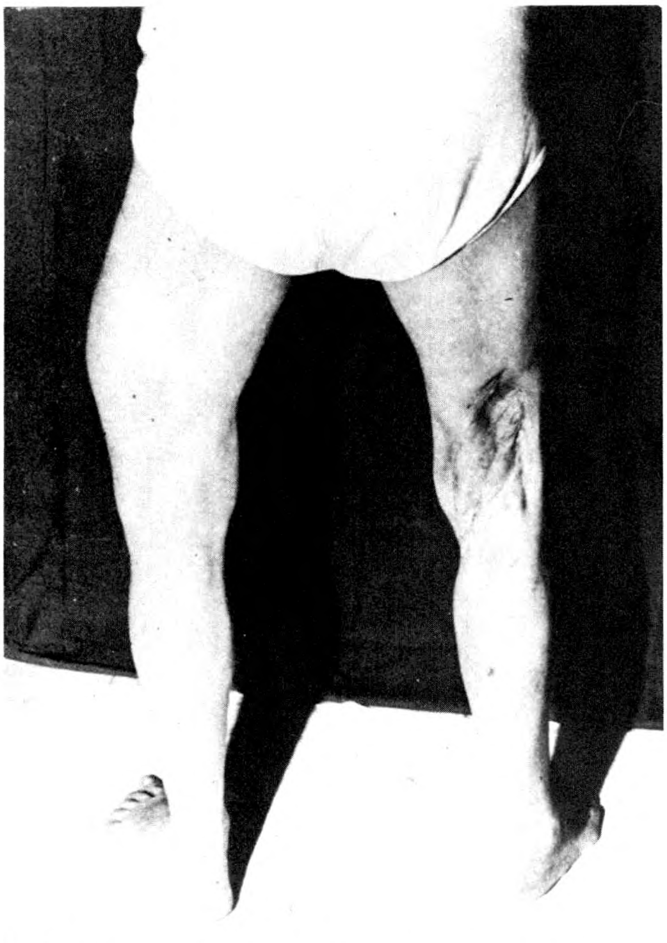

FIG. 2. Five years after the accident the patient is able to stand and to walk without any help.

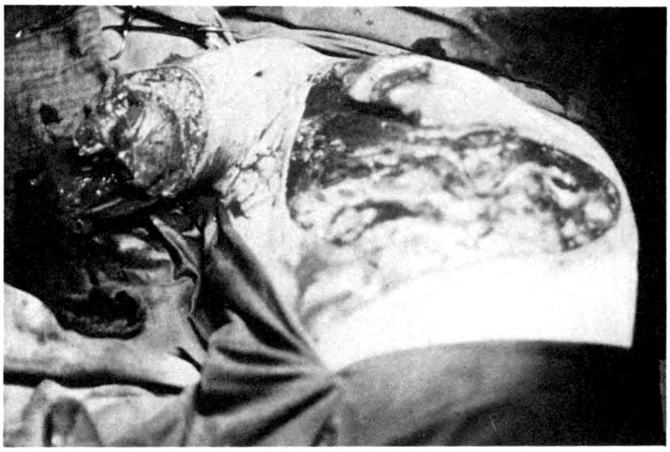

FIG. 3. Appearance of the boys right side on arrival in the hospital. The stump of the right arm is left on the body. The right chest is opened by a deep tangential wound.

tissue temperature to 10°C. During this period both wounds were debrided. The next step was the repair of the comminuted fraction of the humerus, the fragments of which were fixed with screws and a plate. Anastomoses of three small veins (two along the brachial artery and the basilic vein) was followed by arterial anastomoses. Circulation was restored 5 hours after injury. Following the advice of neurosurgeons we did not perform a primary nerve suture. The operation was terminated with fixation of the triceps muscle tendon to the olecranon, suturing of the severely damaged flexor muscle group and covering of the wound with the damaged skin (Fig. 4).

Postoperative Course

Twenty four hours after operation, congestion and cyanosis of the arm occurred. The clinical symptoms of thrombosis of the venous anastomoses were verified during reoperation and the venous anastomoses were redone. After this event we heparinized the patient with 1 mg./Kg./6 hours for 5 days. The necrotized skin area was replaced with autotransplants 4 weeks after injury. Secondary nerve repair was done 12 weeks later. The procedure was extremely difficult because of severe keloid scar. The continuity of the proximal end of the median nerve could be isolated and communicated with the distal end of a nerve, which was embeded in the scar mass. It was not clear at this point if the distal end was the median or radial nerve. The highly shortened proximal end of the radial nerve was unfit for anasto-

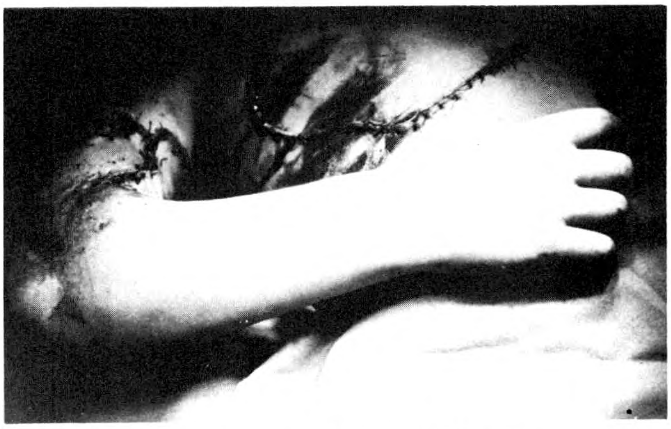

FIG. 4. The end replantation of the arm.

moses. The continuity of both above mentioned nerves was attained after resection of neurinoma. Recovery of neural function seemed to be highly improbable.

Return of Function

Galvanic stimulation and physical therapy were continued after the 4th week. The first active motion which could be seen 6 months after neural repair was extension of the hand and sensibility in the forearm (Fig. 5). Flexion and extension in the elbow joint increased rapidly and remained only slightly limited by scar contraction. The temperature sensibility returned on the posterior surface of the forearm and hand but was absent on the volar surface of the fingers causing a slight scalding with boiling water 6 months ago.

Present Status

Severe keloid has developed in all scars, especially in the upper arm extending to the forearm. The right forearm has the same color and length as the left forearm except that it is slightly thinner (Fig. 6). Sensibility has returned to the posterior and anterior surface of the forearm and the dorsal surface of the hand but it is absent on the volar surface of the fingers. Active motion of the elbow joint is nearly unrestrained. All functions of the radial nerve are evident (Fig. 7). One and a half year after neural suture we could detect an active flexion of I–III fingers. The boy can pick up minor objects with the three fingers as well as carry his brief case (Fig. 8). He is able to ride his bicycle and to hold on to the handlebars with only his right hand. There is no return of function of the thenar and hypothenar muscles now in the function of the ulnar nerve.

Discussion

The late results of our two replanted extremities demonstrate clearly that the efforts to preserve an extremity amputated by trauma can lead to full or partial restitution of function. The extent to which the replanted extremity regains its function depends upon the degree of tissue damage and also on the primary operative procedure. Several factors which are of importance are discussed.

Time Factor: The quick restitution of circulation is important to avoid an ischemic muscle contraction and to attain proper function of the extremity eventually. Circulatory function can be attained promptly by reducing the ischemic time during the primary operative procedure as well as by prolonging the tolerance time against hypoxia with technics of preservation. In normothermia, extremities have been replanted successfully 6 hours after

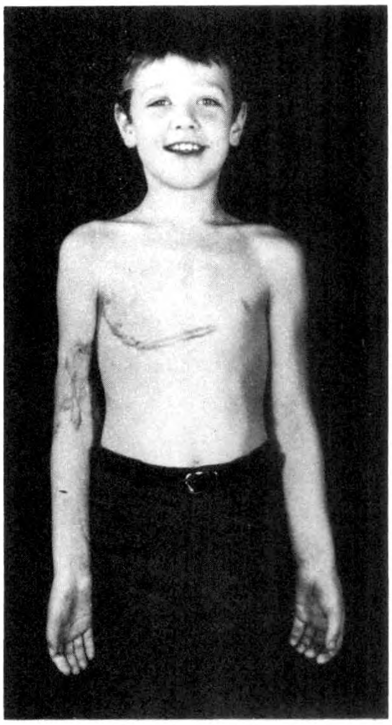

FIG. 6. The patient 24 months after replantation. Severe keloid has developed in all scars.

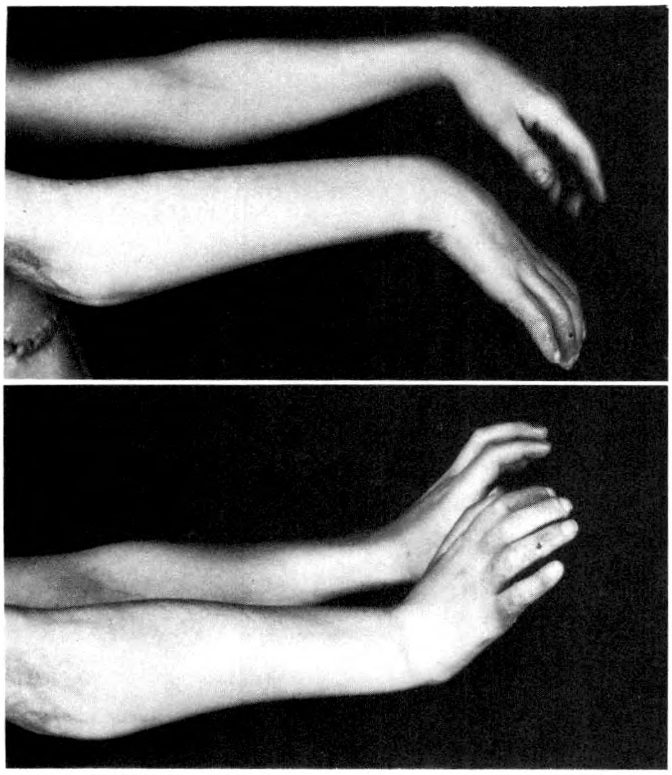

FIG. 5. Nine months after the secondary neural repair the boy can actively extend the wrist.

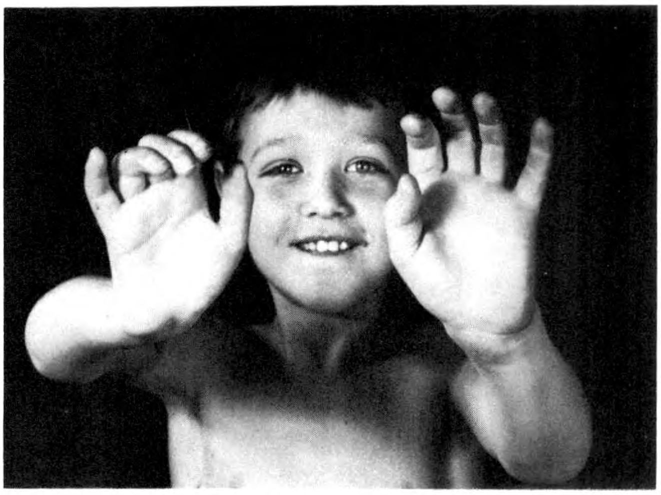

FIG. 7. Twenty four months after replantation. All functions of the radial nerve have returned.

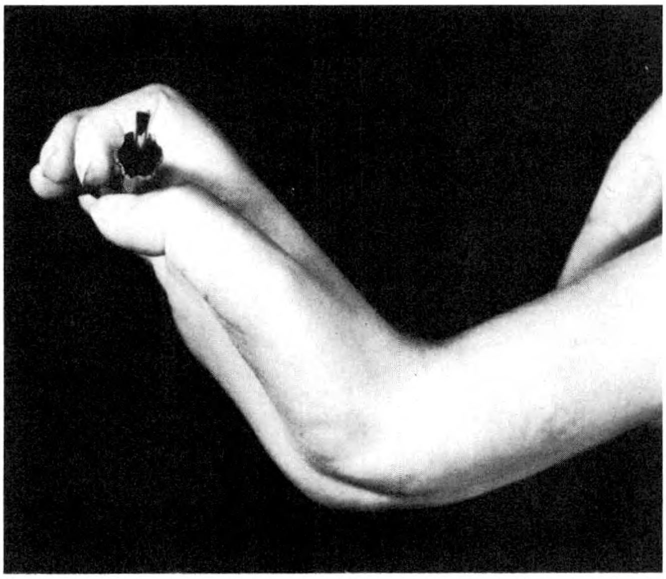

FIG. 8. Beginning active flexion of the thumb, the index and middle finger: minor objects can be picked up.

amputation has occurred.[1] Some authors state that the tolerance time after interruption of circulation in the extremities is between 8–12 hours.[4] This time can be extended to 18 hours with surface hypothermia by immersion in ice water.[6] The ischemic time in the second patient was 5 hours by hypothermia. In both patients no ischemic muscle contractions could be seen. Debridement of necrotized soft tissue and covering of skin lesions with skin autografts is important to avoid infection and serious contraction by scar. In both patients the skin lesions were primarily covered with severely damaged skin that was replaced some weeks later by autotransplants. Because of a tendency to form keloid the second patient developed a scar contraction at the anterior surface of the elbow joint, which has to be corrected by a later operation.

Bones: Exact anatomical reconstruction and sufficient fixation of the fragments during the primary operative procedure are important to avoid pseudarthroses postoperatively. The osteosyntheses can be achieved by nailing as well as by plates and screws. Only in special instances as with our first patient can an extracutaneous fixation with traction be used. Some authors recommend a shortening of the bone of 2–4 cm. to eliminate tension in the anastomoses of nerves and vessels.[4,5,6] Although the growth of replanted limbs seems to be retarded, in our opinion, shortening of the bone is not necessary. No shortening of bones was done in either of our patients and all anastomoses were constructed without tension.

Vascular: Adequate arterial anastomoses as well as sufficient venous anastomoses determine to a large extent the early and late results, especially since the lymphatic vessels are interrupted during the first postoperative period. Small venous anastomoses have a tendency to be thrombotic and it became necessary to heparinize the patient as in our second case. From the three venous anatomoses that were performed during the first operation, only the basilic vein remained patent and provided venous outflow (Fig. 9). Severe swelling of the arm and leg disappeared after 2 weeks probably due to the development of new lymphatic vessels.

Nerves: The type of neural suture, the time of nerve repair and the activation of the neuro-muscular system during the postoperative period are very important to the ultimate outcome. The most discussed issue is the

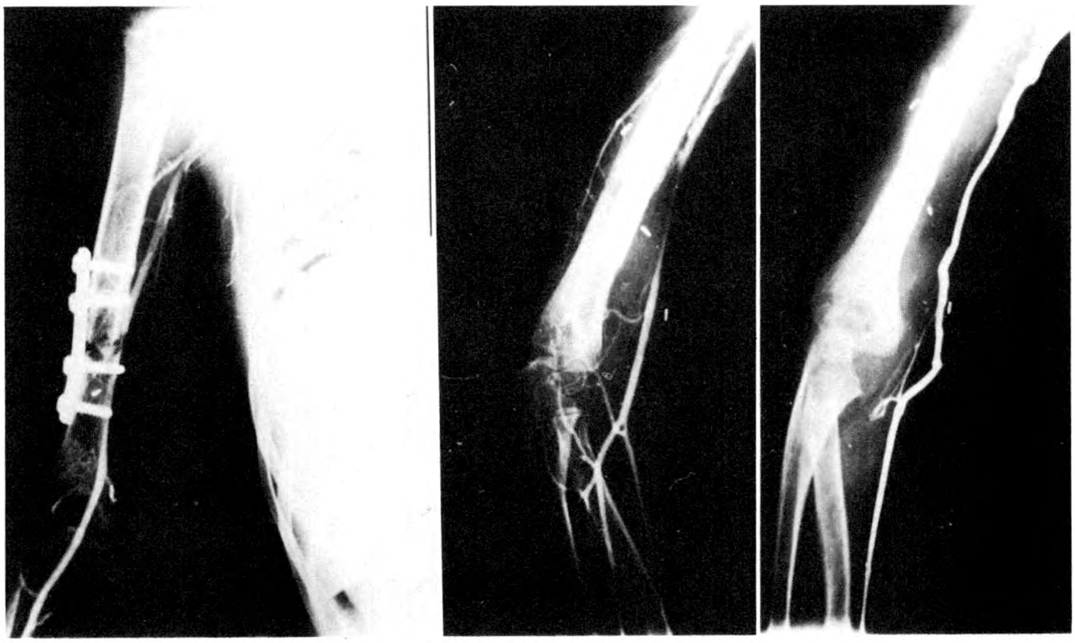

FIG. 9. Angiogram of the arm 3 months after replantation showing the artery and the venous drainage only through the basilic vein.

time of nerve repair. Although some authors favor a secondary neural suture,[3] most investigators agree that a primary suture is particularly suitable for the replantation of upper extremities. Primary sutures facilitate the anatomic preparation of the nerve ends and eliminate the need for extensive resection of nerve ends by secondary suture because of neurinomas. Malt[6] reports two cases of replanted upper extremities. In the first case the functions of the ulnar and median nerves returned 20 months after primary neural suture. In the second case, 8 months after operation, only the functions of the radial nerve were noted. In our first patient the functions of the tibial nerve could be observed 1½ years after primary neural suture. Conversely, the peroneal nerve showed no signs of regeneration. Only one replantation of a lower extremity has been reported by Close and Gilbert.[2] In this instance the sciatic nerve was intact. Therefore a comparative study with our results is not possible.

The secondary neural suture in our second patient which was done 12 weeks after the accident only with the ulnar and median nerve was extremely difficult. The upper ends of the ulnar and median nerve which had been marked during the first operation could not be prepared and adapted to the anatstomoses because of the scar tissue. There existed some doubt during the operation whether the distal end of the median or radial nerve could be anastomosed to the proximal end of the median nerve. Six months after the secondary suture a partial return of sensibility and motor function with active extension in the hand joint has occurred. Therefore, it is certain that the distal end of the radial nerve has been anastomosed to the proximal end of the median nerve.

The degree of function that has returned 2 years after the secondary neural suture can not be explained completely. The function of the radial nerve has returned completely in addition to a definite active flexion of the first three fingers enabling the lifting of minor things. During the suturing of the nerves only the ends of the ulnar nerve and probably the proximal end of the median nerve with the distal end of the radial nerve were connected, therefore, it can be assumed that the neuromuscular innervation is abnormal.

Although in both instances a partial return of function in the extremities has been achieved we believe that a primary neural suture must be preferred for following reasons:

a) the preparation of the nerve ends in the extensive scar tissue is difficult,
b) the resection of the terminal nerve ends leads to a shortening of the nerves,
c) the results of a secondary neural suture are not as successful as a primary neural suture.[4,12]

In the upper extremity the ulnar nerve and in the lower extremity the peroneal nerve seem to have the least ability to regenerate. Another factor necessary to achieve good function in the replanted extremity is the activation of denervated muscle groups during the first year until the reinnervation of the muscles occurs. This is important to avoid atrophy caused by inactivity. The reward for these difficult and time consuming efforts is the restitution of good function of the limb, the rehabilitation of the patient, and the elimination of any need for a prosthetic device.

Summary

The ultimate results of successful replantation of upper and lower extremities are reported. In the first case a leg of an adult man was almost completely amputated. Five years after primary neural suture the leg has good motor and sensory reinnervation. The man is able to walk without any help. In the second case the arm of a young boy was severed. Two years after secondary neural repair all functions of the radial nerve and a partial function of the median nerve are present.

We favor primary neural suture rather than delayed neural repair because the nerve ends can be adapted much more easily and resection of grown neurinomas is not necessary.

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Calcium, Phosphorus, and Magnesium Metabolis
Following Head Injur

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DIVALENT ION METABOLISM (calcium, phosphorus, and magnesium) following injury has not been studied as extensively as that of the monovalent ions (sodium, potassium and chloride). The available reports delineate few definite trends among all the studies. Serum levels of calcium, phosphorus and magnesium have been noted to increase, decrease or remain unchanged.[2-5,12,14,15,17] Urinary excretion of these divalent ions has been noted to be unaffected or to exhibit varying periods of retention and diursis.[4,5,12-14,17,18,21] Patients undergoing general operation develop magnesium deficiency very frequently.[14] In previous studies we did not find monovalent ion excretion in neurosurgical patients to be different from that reported after general injury and operation.[7] We have examined the excretion of the divalent ions (calcium, phosphorus, and magnesium) in patients with head injuries and detail the findings in this report.

Materials & Methods

Three Experimental Groups were Studied:

A.) *Normal Controls.* Eight healthy young adults were maintained on a diet of fixed mineral composition (calcium 1200 mg. phosphorus 1200 mg., magnesium 300 mg. daily) for a period of 12 days. They were ambulatory but remained in a hospital environment on the General Clinical Research Center. Urines were collected during the last 5 days of the period.

B.) *Normal Volunteers.* Seven healthy young adults remained at bed rest and received the same intravenous electrolyte solution given to the patients with head injury (*vida infra*). Discomfort to the subjects precluded extension beyond 3 days. In the normal volunteers and normal controls urines were collected by spontaneous voiding and kept refrigerated until the 24-hour collection wa completed.

C.) *Head Injury Patients.* Seven patients with moderate to severe head injury but no other major bodil injury were studied (Table 1). Criteria for acceptanc into the study and method of grading the degree of injury have been outlined previously.[8] They received balanced electrolyte solution that contained in each liter 100 Gm. glucose, 23 mEq. lactate, 25 mEq. sodium, 2 mEq. potassium, 36.2 mg. magnesium and 89.5 mg phosphorus. Two liters were given each 24 hours. Exigencies of caring for critically ill patients interfered wit this in some instances. All patients were started on th study within the first 12 hours after injury. The first complete 24-hour period after starting the first urine collection was designated Day 0, the second 24-hour perio Day 1, etc. Urines were collected by indwelling urethra catheters into closed-drainage plastic bags that wer changed every 4 hours. The bags were kept refrigerate until urine was pooled in 24-hour collections and an aliquot acidified with hydrochloric acid. Because of th short time period of 4 to 5 days, no attempt was mad to collect stools.

Sodium and potassium were determined by flam photometer (Coleman), and phosphorus by the molybdate reaction in the Technicon autoanalyzer. Magnesiu and calcium were determined by fluorimetry[6] and nitrogen by the micro-Kjehldahl method.

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TABLE 1. *Data on Neurosurgical Patients Studied*

Patient	Length of Coma	Trauma Grade	Serum Values—mg/100 ml.*						Final Balance for Study**				Days in Study	Clinical Data
			Day 0***			Day 2								
			Ca	P	Mg	Ca	P	Mg	Ca	P	Mg	Nit		
1. M. W.	4 mos.	III	9.31	3.60	1.38	7.91	1.93	1.78	−501	−3868	−177	−75.7	5	19/M brain stem contusion
2. D. G.	25 days	III	9.60	2.83	1.67	8.63	2.18	2.17	−208	−2321	+44	−60.7	5	23/M brain stem contusion
3. R. A.	24 days	II	8.40	1.21	1.67	9.20	1.38	2.03	−418	−2883	−183	−78.2	4	32/M cerebral contusion & skull fracture lt. frontal & rt. temporo-parietal
4. P. T.	11 days	III	9.81	2.84	1.87	10.45	1.73	1.96	−242	−1275	+49	−23.0	4	19/F cerebral contusion (rt. hemisphere)
5. S. G.	5 days (died)	III	7.90	1.55	2.18	8.42	2.94	2.18	−209	−1689	−13	−28.6	4	18/F acute subdural hematoma & contusion lt. hemisphere
6. M. S.	4 days (died)	II	10.37	2.70	1.32	9.63	2.83	2.76	−73	−1782	+83	−66.5	4	22/M cerebral contusion (rt. frontal & lt. occipital), intracerebral hematoma (basal ganglia)
7. J. R.	48 hrs.	II	8.07	2.55	1.76	7.89	2.07	1.58	−613	−1716	−28	−39.2	4	18/M cerebral contusion basilar skull fracture

* Ranges for serum electrolytes in 20 apparently healthy personnel: calcium 9.08–10.48 mg./100 ml., phosphorous 2.26–4.50 mg./100 ml., magnesium 1.80–2.40 mg./100 ml.

** These are not true balances because stool excretion was not measured (See text for details). Calcium, phosphorus and magnesium are in mg.; nitrogen is in Gm.

*** Day 0 is the day of injury.

Results

1) *Serum Levels*—Table 1

All patients had low serum levels of one or more of the divalent ions during the study. Initial serum calcium levels were below 9.00 mg./100 ml. in R. A., S. G., and J. R. Changes in serum levels by Day 2 showed no consistent trend, being higher in three patients and lower in four. Only three of the patients had values above 9.00 mg./100 ml. by Day 2. These changes did not relate to serum protein values nor to urinary calcium excretion. The initial serum phosphorus levels were low in R. A. and S. G. The levels which fell during the study in four patients, were below 2.26 mg./100 ml. in five patients on Day 2. Initial values for serum magnesium were below 1.80 mg./100 ml. in five of the seven patients. By Day 2, the levels had increased in five patients but decreased in two others. No patient exhibited signs or symptoms which could be attributed to any changes in serum electrolytes. The serum values in the normal volunteers were always within normal limits.

2) *Urine Excretion*

a) *Calcium* (Figs. 1C, 2 and Table 1). None of the patients received calcium during the study. Urinary excretion on the day of injury was less than 70 mg. in all except R. A. and P. T. In these two patients urinary calcium decreased daily with total calcium losses of 418 mg. and 242 mg. during the study (Table 1). In J. R. and M. W. there was a progressive increase in daily calcium excretion with total calcium losses of 613 mg. and 501 mg. The other three patients had slight increases in calcium excretion on Day 2 with progressive decrease thereafter. The overall losses of these patients which were much smaller, were as low as 73 mg. in 4 days in M. S. Average balances (intake minus urine excretion) per day for the study varied from −18 mg. to −153 mg.

b) *Phosphorus* (Figs. 1C, 2 and Table 1). With a minimal intake of 100 to 200 mg./day, all except D. G. had "phosphate diuresis" on the day of injury. The general trend was toward a continuing decrease in urine phosphorus with an increase on Day 3 or Day 4. Despite the low phosphorus excretion on Day 2, only one patient achieved a positive balance. Average balances (intake minus urine excretion) per day for the study varied from −319 mg. to −774 mg.

c) *Magnesum* (Figs. 1C, 2 and Table 1). Magnesium intake was 40 to 90 mg./day. On day of injury urine magnesium was less than 90 mg. in all patients. Only J. R. had a negative balance. The general trend was toward an increase on Day 1 with a progressive decrease for the next 2 days. Final magnesium balances (intake minus urine excretion) were positive in three patients and minimally negative in two others. Average balances per day for the study varied from +21 to −46 mg.

3) *Inter-ion Relations*

Correlations of the patients' urinary excretion of calcium, magnesium, phosphorus, sodium, potassium, nitrogen and water with each other were calculated. No significant relation occurred between sodium and calcium excretion. Calcium excretion did correlate significantly with magnesium excretion ($r = 0.39$, $p < 0.025$) and magnesium with sodium ($r = 0.31$, $p < 0.05$). Nitrogen excretion correlated with potassium ($r = 0.70$, $p < 0.005$), with phosphorus ($r = 0.48$, $p < 0.005$), and with magnesium ($r = 0.28$, $p < 0.05$). Urine volume correlated only with sodium excretion ($r = 0.43$, $p < 0.025$).

4) *Group Comparisons*

In comparing the normal volunteers to the patients, both of whom received similar intravenous fluid and electrolyte rations, the notable differences were in the serum values and the pattern of urinary excretion of the divalent ions (Fig. 1 and Table 2). The serum values for calcium, phosphorus, and magnesium remained within the normal range throughout the study in the normal volunteers, but varied considerably within and between patients (*vide supra*).

In the normal volunteers there was a progressive fall in urinary excretion of the divalent ions. This was marked in calcium, less so in magnesium and hardly discernible in phosphorus. In the patients this progressive fall was most marked in phosphorus excretion. Both calcium and magnesium excretion were less on Day 0 than on subsequent days. Calcium excretion then seemed to rise to the excretory level for the volunteers for the particular day in question, while magnesium rose to much higher levels. When comparing daily urinary excretion between the two groups (volunteers and patients) with the *t* test (Table 2), only calcium excretion was different on Day 0. On Day 1 both magnesium and phosphorus were significantly different. On Day 2 only magnesium excretion differed. When the average balances (intake minus urine excretion) per day for the 3 days were compared by the *t* test, no significant differences were noted between the patients (P) and the volunteers (V), *i.e.*, calcium: P −75 ± 16.3 mg./day, V −117 ± 21.7 mg./day; phosphorus: P −528 ± 92.9 mg./day, V −355 ± 80.8 mg./day; magnesium: P −2.6 ± 10.1 mg./day, V +17.3 ± 7.0 mg./day.

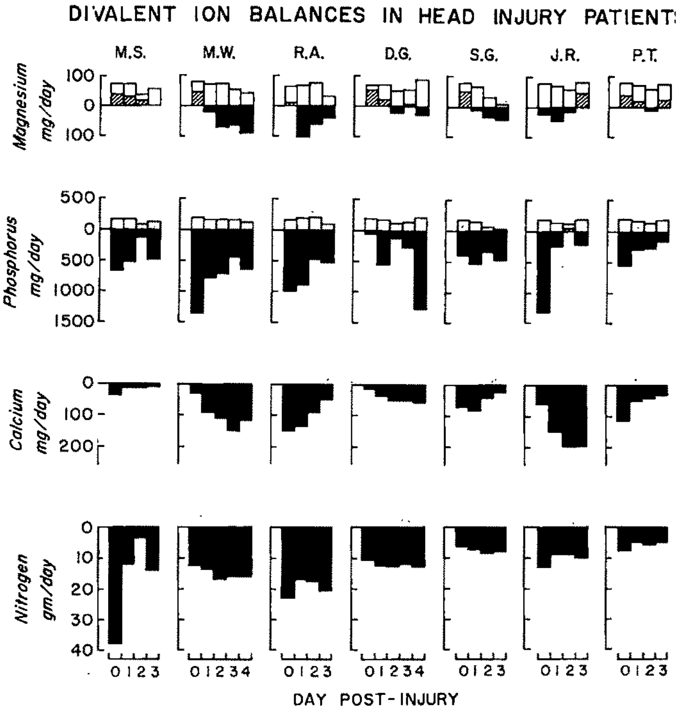

FIG. 2. Calculated balances (intake minus urine excretion) for each patient. Day 0 is the day of injury. Intake is graphed upward from the zero balance line and output downward from the top of the intake line. A crosshatched area above the zero line indicates positive balance. A darkened area below the zero line indicates negative balance. There was no intake of calcium or nitrogen.

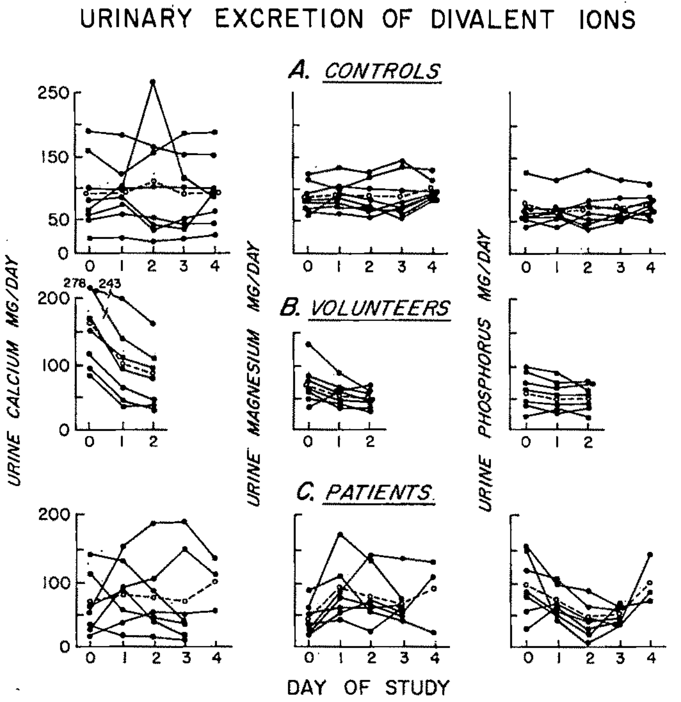

FIG. 1. Daily urinary excretion for all individuals in all groups. The dashed line with open circles is the mean for each group. Numerical value for each mean and its standard error is given in Table 2. In the patient graphs, (C), excretion for each patient can be identified using the numbered listing from Table 1. Reading from top to bottom on Day 0 the patients are: for calcium—3, 4, 5, 7, 6, 1, 2; for magnesium—7, 3, 4, 6, 1, 5, 2; for phosphorous—1,7,3,6,4,5,2.

Discussion

The patients are few in number, but the type of injury was specific, and the mode of treatment was uniform, i.e., observation and supportive therapy. The typical post-injury response in sodium and potassium (data not tabled) and nitrogen excretion occurred in these patients; hence, we assume they were not undergoing any unusual metabolic response to trauma.[7] None of the patients had extrarenal losses of calcium, phosphorus, or magnesium, and in this short-term study no excessive losses of electrolyte were demonstrated. Maximum losses in the 4 to 5 day period (intake minus urine excretion) were calcium 613 mg., phosphorus 3868 mg., and magnesium 183 mg. None of the values have ben corrected for nitrogen loss. Average daily balances for the immediate post-injury period were not different from normal healthy volunteers on the same regimen of intravenous fluid and electrolytes.

TABLE 2. *Daily Urinary Excretion of Divalent Ions in All Groups*

	Day 0*			Day 1			Day 2			Day 3			Day 4		
	Ca	Mg	P	Ca	Mg	P	Ca	Mg	P	Ca	M	P	Ca	M	P
A Control (8)	93	88	710	94	91	674	110	87	673	90	88	700	94	98	736
	19.6	7.2	85	16.9	7.2	81	30.2	9.0	95	20.9	10.9	81	19.5	6.1	72
B Volunteers (7)	164	68	616	103	53	487	81	45	489	—	—	—	—	—	—
	27.0	12.0	96	22	6.3	79	19.0	5.0	71	—	—	—	—	—	—
C Patients (7)	68	43	950	81	87	710	77	79	400	73	64	500	103	88	1000
	18.5	9.3	180	19.2	16.8	90	23.5	15.8	110	27.4	12.6	40	23.7	32.7	240
A vs B	<.05	ns	ns	ns	<.005	ns	ns	<.005	ns	—	—	—	—	—	—
A vs C	ns	<.005	ns	ns	ns	ns	ns	ns	<.05	ns	ns	<.05	ns	ns	<.05
B vs C	<.01	ns	ns	ns	<0.05	<.05	ns	<.05	ns	—	—	—	—	—	—

* Day 0 is day of injury. Urine values are the mean and SE in mg./day. Numbers in parentheses are the subjects in each group. See text for definition of groups. Probability values were obtained by *t* test between groups as indicated.

Stool excretion must be considered in any extended study of divalent ion metabolism. It is questionable whether any significance can be attached to analysis of stools collected over a short period of time. In the few postoperative studies in which stool was analyzed, the excretion of calcium and magnesium was found to increase[13] or to remain proportionately the same as preoperatively.[4,12] Under ordinary circumstances with all oral intake, stool losses as a fraction of intake are calcium ⅘, magnesium ⅔, and phosphorus ⅓. In patients with no oral intake, net stool excretion is dependent on endogenous intestinal secretion of electrolyte which may vary from patient to patient. In a group of fasting patients with no oral intake except water, average stool excretion has been observed to be calcium 115 mg./day, phosphorus 94 mg./day, and magnesium 21 mg./day.[9] Assuming that there was the same range of intestinal secretion in patients with head injuries the only balances reported here which might be changed significantly would be calcium.

The urinary excretion pattern for magnesium noted in this study, *i.e.*, low excretion on the day of trauma, which increases over the next 1 or 2 days to exceed intake, followed by decreasing excretion has been described by several investigators.[4,12,17,18] This may be the typical post-trauma pattern. Mark and Hayes describe no change in urine magnesium, and Sawyer *et al.* describe a progressive decrease in urine magnesium.[13,14] Decrease in serum magnesium after operation occurred in 56% of patients studied by Heaton, and almost 100% of those described by Sawyer.[4,14] Decrease in serum magnesium was also described by Broughton and Scheinman.[2,15] Thoren, however, noted little change in serum magnesium levels following moderate trauma, but an increase following severe trauma.[17] Although the serum magnesium in our patients fluctuated, no specific pattern could be described.

Urinary calcium excretion following operation has been described as unchanged or as exhibiting a specific pattern of calcium retention the day of operation with a calcium diuresis over the next 2 days.[13,21] Urinary calcium patterns in our patients were varied. Some followed the pattern described by Wynne, while others were just the opposite.[21] It is notable that in all three experimental groups studied by us, calcium excretion was more variable than either magnesium or phosphorus. Most authors describe serum calcium as being unchanged in the immediate post-trauma period.[2,15,17] Clowes *et al.* described a fall in serum calcium during operation with a return to control levels by the second to fourth day.[3] This change was attributed to a fall in ionized calcium associated with a rise in inorganic phosphate levels. For the most part our patients had serum phosphorus levels that were low, and the serum calcium levels showed no consistent changes.

Urinary calcium and magnesium are affected by nutrient ingestion, diurnal variation, intake and excretion of other ions especially sodium, activity, acidosis, alkalosis and various hormones and vitamins.[19] Magnesium deprivation leads to a progressive decrease in urine magnesium until the fourth day when the urine magnesium is minimal.[16] As suggested by Heaton, this could be invoked to explain only the decreased excretion on the day of injury. However, a more plausible explanation for this decrease on the day of injury would be the decrease in glomerular filtration rate and renal blood flow that occurs immediately after injury. The post-injury changes in magnesium have been attributed to hyperaldosteronism.[2,18] Short-term administration of aldosterone, however, has no effect on magnesium excretion.[10] It is difficult to postulate any endocrine effect at all in view of the fact that the typical post-injury pattern for magnesium has been described after bilateral adrenalectomy, hypophysectomy, and parathyroidectomy.[1] Walker found that magnesium excretion correlated with nitrogen excretion which was true in our patients also.[18] Heaton demonstrated that the magnesium "diuresis" phase could be blocked by supplying adequate calories along with normal organic and inorganic dietary constituents.[4] This is the opposite of non-injured patients, in whom the administration of glucose, galactose, protein, sodium and calcium will increase urine magnesium.[11] If it were merely a matter of inadequate nutrients the normal volunteers should have shown the same pattern.

The patients with a progressive fall in urine calcium may have had normal responses to calcium deprivation. Cortisol increases urine calcium and when elevated post-injury may contribute to the "calcium diuresis" seen in some of the patients. Only the three patients who exhibited a "calcium diuresis" pattern had serum levels decrease to below normal as they progressed in time from injury. This would suggest that the renal tubule was not responsive to the usual mechanisms for calcium conservation. Even though calcium excretion has been closely correlated with sodium excretion in many clinical and experimental situations, we could demonstrate no such correlation in these patients.

Urinary phosphorus excretion pattern in our patients was similar to that described by Wynne, *i.e.*, phosphorus "diuresis" on the day of operation followed by phosphorus retention.[21] This may be a typical post-trauma pattern. Insufficient studies have been published to verify this, however. Under normal circumstances urinary inorganic phosphorus excretion is principally related to dietary intake, renal function, and parathyroid hormone secretion rate. Other factors play a role depending on the circumstances.[20] Cortisol causes increased urinary excretion of phosphorus, as does glucose loading. Insulin and growth hormone, however, have the opposite effect. Many patients with severe head injuries have respiratory alkalosis which will cause low serum phosphorus and decreased urine phosphorus excretion. As yet, no evidence is available to indicate whether injury can either stimulate or depress parathyroid gland function.

In the post-injury state cortisol and growth hormone secretion are elevated. Vasopressin release, glucose intolerance, and variable changes in insulin secretion develop. A marked catabolic response with increased caloric demand and increased oxygen consumption occurs. Renal blood flow and glomerular filtration decrease. In addition, the patient's fluid, electrolyte and nutrient ingestion are distorted or omitted. At various times post-injury (measured in hours) one phenomenon may play a dominant role only to recede in importance a few hours later. The metabolism of the divalent ions calcium, phosphorus and magnesium in the head-injury patients we studied did not differ from what has been described in patients following general operation and injury suggesting that head injury *per se* has no specific effect on the excretion of these ions. The frequent description of hypomagnesemia and magnesium deficiency in postoperative patients has been in those patients with bowel disease. A period of gastrointestinal fluid losses (vomiting or diarrhea) and poor nutritional intake preceded operatio followed by a period of prolonged parenteral feeding This situation would occur rarely if at all in head-injure patients. Those who remain in coma for prolonged periods can receive adequate nutritional intake via tub feedings. We conclude, therefore, that there is minima distortion of divalent ion metabolism in the immediat period after head injury and no special provision i necessary for these ions in the metabolic care of the patient during that period.

Summary

Serum and urine levels of calcium, phosphorus an magnesium were measured in seven patients with moderate to severe head injuries for 4 to 5 days post-injury A control group of seven healthy adults remained at be rest, received the same intravenous solutions as th patients with head injuries, and underwent the sam chemical determinations. Serum levels of these ions remained in the normal range in the control group. In th patients the levels of serum calcium were below 9.0 mg./ml., serum phosphorus was below 2.26 mg./100 ml and serum magnesium was below 1.80 mg./100 ml. in 50 of the determinations. A recognizable "post-injury pattern" was discernible for urinary excretion of magnesiu and phosphorus in the patients. This pattern appeare to be no different from that described in patients afte general operation or injury, suggesting that head injur *per se* has no specific effect on the excretion of thes ions. No pattern for urinary excretion of calcium was apparent. No excessive loss of any of these ions occurre during the study. Our data would suggest that in patient with head injury no special provisions for the replacement of calcium, phosphorus and magnesium are necessary in the immediate post-injury period.

Acknowledgment

The authors greatly acknowledge the technical assistance o Miss Joan Brielmaier, R.N. in the completion of these studies.

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Book Review

Surgeon to Soldiers. Diary and Records of the Surgical Consultant Allied Force Headquarters, World War II, by Edward D. Churchill, M.D., John Homans Professor Emeritus of Surgery, Harvard University; former Chief, General Surgical Services, Massachusetts General Hospital, Boston. J. B. Lippincott Company, Philadelphia and Toronto, 1972. Library of Congress Catalog Card No. 72-157864.

THIS book is based on the author's experience while serving as Surgical Consultant to Allied Force Headquarters in the North African and Mediterranean Theaters of World War II. On leave of absence from his responsible position in Boston, he arrived in Algiers to take up his new duties in early March 1943. His overseas service, lasting about two and one-half years, covered the latter part of the Tunisian campaign, the Sicilian campaign and the liberation of Italy. The book draws freely on the diary and records which the author carefully maintained and on a varied assortment of eyewitness reports, case reports, personal letters and official memoranda and documents. In essence it is an informal, colorful and highly personal account of what the author saw, did and thought during the course of his brilliant career as a surgical consultant. The book is lightened by parts which read like a travelogue or adventure story. The subject matter is divided into five sections, headed Medical Mobilization, North Africa, Sicily, Italy and the Last Phase. Epilogue, Appendixes and Bibliography conclude the work. The material appears only roughly in chronologic order, however, and the narrative is interrupted by chapters on specific topics such as Prisoners of War, Diary and Letters of a Forward Surgeon, German Soldier's Diary after El Alamein, Penicillin in Tripoli, Cold Injury, and Gas Gangrene.

It was soon clear to the author on his arrival at the Algiers headquarters that the North African Theater was likely to be a "learning" (and teaching) theater, a laboratory for the testing of new ideas in World War II. This was to hold true not only for medicine and the care of the wounded but for many of the tactical operations. The section of the book dealing with this theater is therefore of special interest. Medical personnel arriving in North Africa early in 1943 found themselves hampered by shortages of help and equipment, inexperienced in battle surgery and by lack of foresight and planning by the Army staff. A rational evacuation system for the wounded and an understanding of priorities and timing in the care of battle wounds had to be worked out. Triaging was therefore at best only rough. No provision had been made for blood transfusion, which at that time was considered by the Army as an impractical and undesirable measure in the combat zone. Plasma was available only in limited supply. Opinion varied as to the best management for burns and as to the proper place for the sulfa drugs in wound management. Out of this primary experience was gradually to evolve in the North African-Mediterranean Theater a superb system of care for the wounded, a process for which the author was in no small part responsible. In time there became available a sufficient number of able young surgeons, men with sound surgica training who could quickly grasp the fundamentals of military surgery. Wound shock was recognized as hemorrhagic shock and was treated by blood transfusion as well as plasma even in the forward zones. Adequate débridement rather than wound "trimming" became standard practice. Delayed primary closure of wounds as well as secondary closure came into effective use When gas gangrene became a problem in the Italian campaign the cases were intensively studied and a rational plan of management was soon forthcoming.

The academic aura surrounding medical care and notable in progressive degree in the North African-Mediterranean Theater was evidenced at first in "Circular Letters" of information and advice going out from headquarters to all medical officers. The author and his associates were continually making rounds in the widely distributed hospitals, observing, discussing problems learning and advising. Later in the War a medical center was set up in Naples with seminars, discussion groups demonstrations and formal medical meetings. Specialized hospitals were assigned to handle such cases as maxillofacial wounds, skull wounds, wounds of peripheral nerves and eye wounds. Finally, it became possible to carry out formal biochemical studies on the acutely wounded and objective data were gathered with reference to wound shock, renal function and acidosis. *A Board for the Study of the Severely Wounded* was created in recognition of the need for a better knowledge of the biochemical and pathological changes in the wounded.

At one point in the book the author reflects on his motives for leaving a responsible position in academic surgery and going off to war. Regardless of his own self-analysis he must have sensed that the active theater of war would present a wonderful opportunity to learn and to teach and under dramatic circumstances to promote a high quality of surgical care. His efforts won him the friendship and appreciation of a substantial group of able young surgeons, an appreciation which still finds expression each year at the annual meeting of the Excelsior Surgical Society.

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The lemon-custard flavor was reported to be pleasant and acceptable to all patients.

*Johnson, L. J. and Landes, J. S.: A clinical experience with an anti-gas laxative in proctologic patients, *Amer. J. Clin. Res. 2*:27, April 1971.

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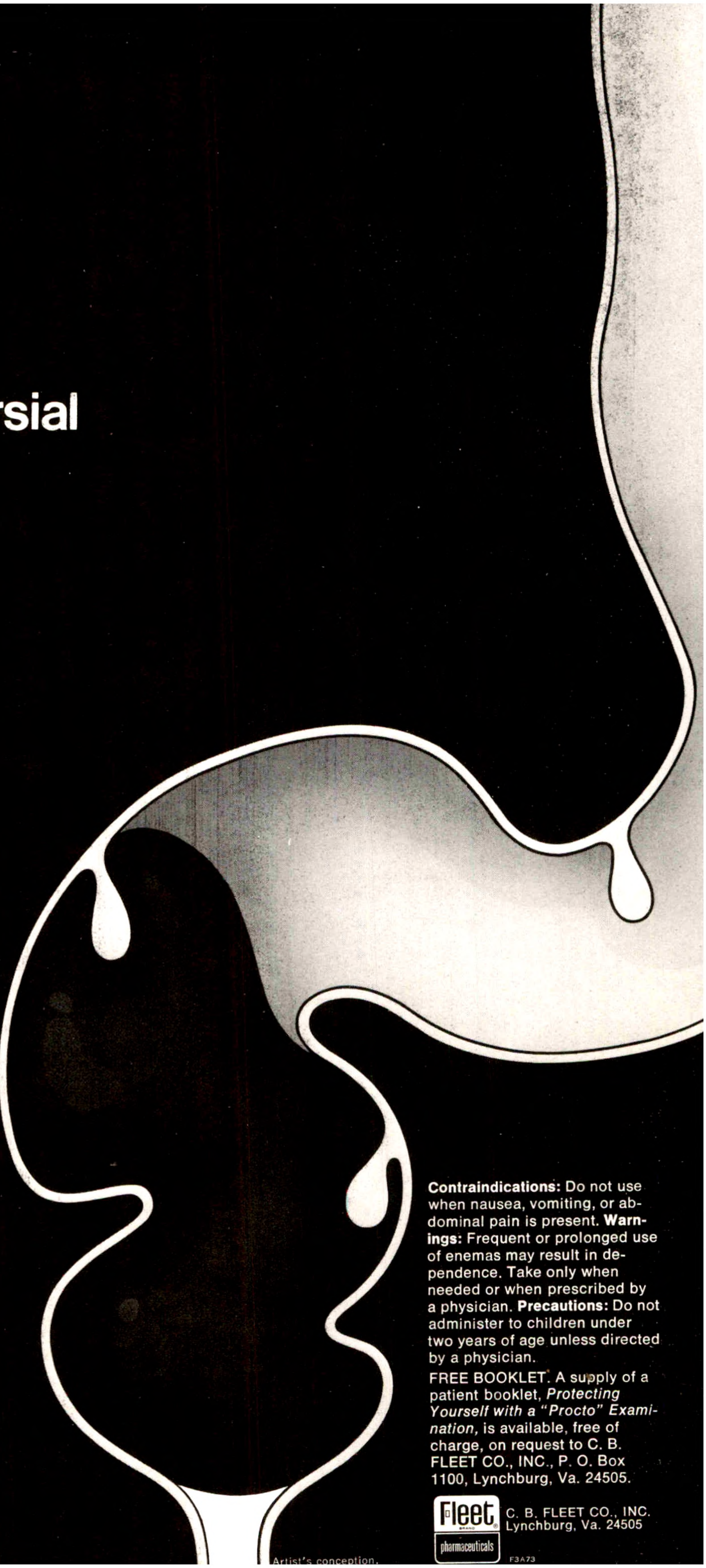

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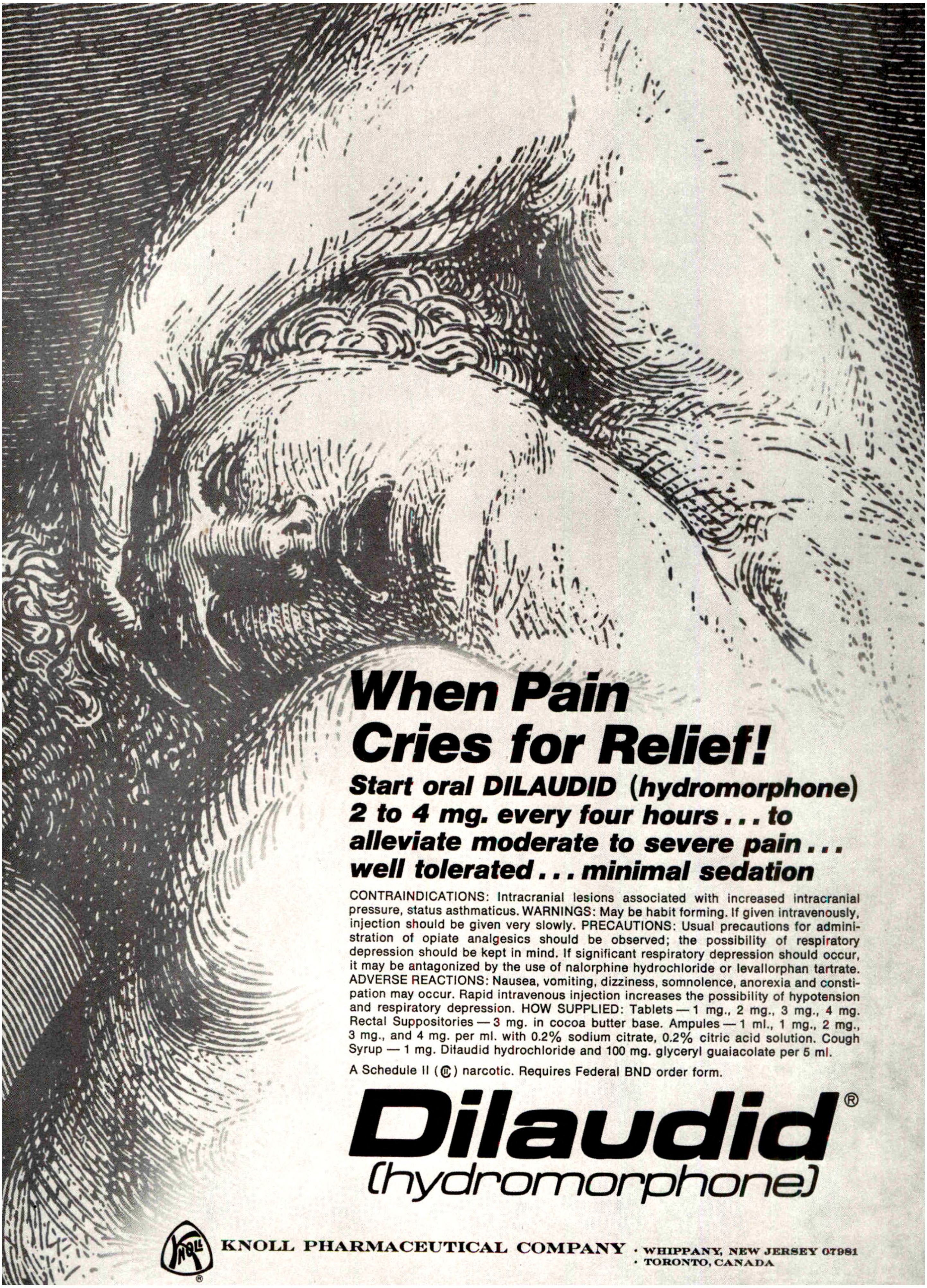

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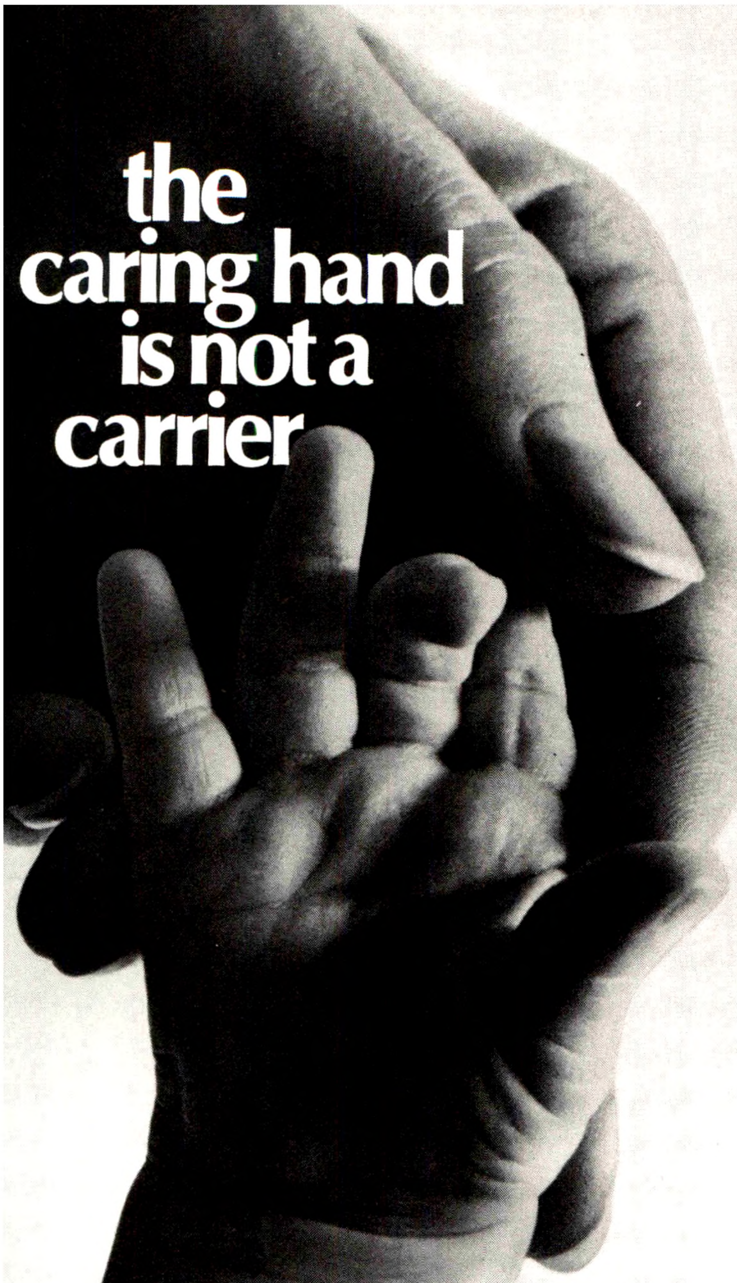

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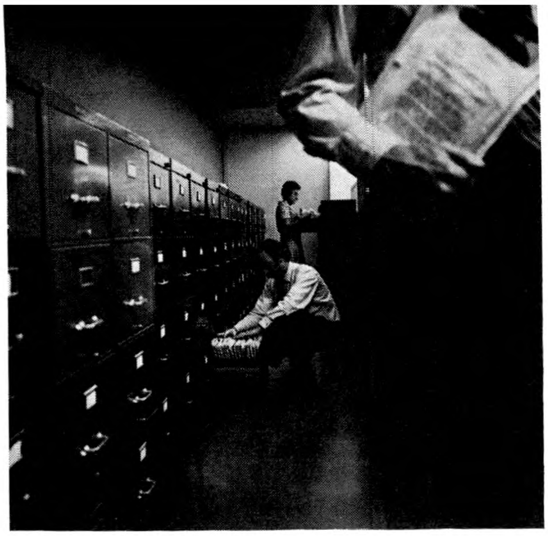

A 10-year, 2500-patient report on the first anti-gas laxative

Unique preparation takes the "pressure" off while it relieves constipation

Ten years of clinical experience with 2200 postsurgical patients and 300 nonsurgical patients have demonstrated the clinical value of a unique preparation for the prevention of postoperative fecal impaction or for routine treatment of functional constipation. The investigators* reported that Laxsil^T.M.^ provided:

More positive laxative action than magnesium hydroxide alone

By reducing surface tension, simethicone assured the spread of magnesium hydroxide in the fecal mass to produce a mild but positive cathartic effect.

Relief of gas distress accompanying constipation

The high surface activity of simethicone tended to change the interfacial tension of gas bubbles, causing them to coalesce and pass out of the GI tract via oral or anal route.

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Laxsil was found to have none of the disadvantages of mineral oil type laxatives or harsh cathartics. Only a few patients experienced a purgative effect. No untoward reactions were seen in any patient.

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*Johnson, L. J. and Landes, J. S.: A clinical experience with an anti-gas laxative in proctologic patients, *Amer. J. Clin. Res. 2*:27, April 1971.

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Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exception should be made with regard to Keflin.

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Precautions: Patients should be followed carefully so that any side-effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keflin occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine, antihistamines, pressor amines, or corticosteroids).

When Keflin is administered to patients vith transient or persistent reduction of urinary output due to impaired renal function, the total daily dose should be reduced. Careful clinical observation and aboratory studies should be made, because higher and more prolonged systemic antibiotic concentrations can occur (see Administration and Dosage below).

When intravenous doses of cephalothin arger than 6 Gm. daily are given by infusion for periods longer than three days, hey may be associated with thrombophlebitis, and the veins may have to be alternated. The addition of 10 to 25 mg. of hydrocortisone to intravenous solutions containing 4 to 6 Gm. of cephalothin may reduce the incidence of thrombophlebitis. The use of small I.V. needles in the larger available veins may be preferred.

Prolonged use of Keflin® (sodium cephalothin, Lilly) may result in the overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest® tablets but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: *Hypersensitivity*—Maculopapular rash, urticaria, reactions resembling serum sickness, and anaphylaxis have been reported. Eosinophilia and drug fever have been reported as associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—Neutropenia and hemolytic anemia have been reported. Some individuals, particularly those with azotemia, have developed positive direct Coombs tests during cephalothin therapy.

Liver—Transient rise in SGOT has been reported.

Kidney—Rise in BUN has been observed; however, some patients with elevated BUN at the beginning of cephalothin therapy have had values return to normal during therapy.

Local Reactions—Pain, induration, tenderness, and elevation of temperature have been reported following repeated intramuscular injections. Thrombophlebitis has occurred and is usually associated with daily doses of over 6 Gm. given by infusion for more than three days.

Administration and Dosage: *In adults,* the usual dosage range is 500 mg. to 1 Gm. of cephalothin every four to six hours. A dosage of 500 mg. every six hours is adequate in uncomplicated pneumonia, furunculosis with cellulitis, and most urinary tract infections. In severe infections, this may be increased by giving the injections every four hours or, when the desired response is not obtained, by raising the dose to 1 Gm. In life-threatening infections, doses up to 2 Gm. every four hours may be required.

In infants and children, the dosage should be proportionately less in accordance with age, weight, and severity of infection. Daily administration of 50 mg. per Kg. (40 to 80 mg. per Kg. or 20 to 40 mg. per pound) in divided doses has been found effective for most infections susceptible to Keflin.

For additional information regarding dosage and administration, see package literature.

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ANNALS OF SURGERY

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Providencia Stuartii *Sepsis:*

A New Challenge in the Treatment of Thermal Injury

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SINCE THE OBSERVATION two decades ago that early death following thermal injury could be largely avoided by vigorous intravenous fluid resuscitation, burn mortality has been primarily associated with bacterial infection of the burn wound with subsequent burn wound invasion. Effective systemic antibiotic administration greatly limited the threat from streptococcal, and later staphylococcal, burn wound infection. In 1961, Tumbusch[6] reported that *Pseudomonas aeruginosa* bacteremia in burned patients had increased in incidence, and shortly thereafter Rabin and associates[4] at the U. S. Army Institute of Surgical Research demonstrated the pathophysiologic structure of gram negative burn wound sepsis, including pseudomonas invasion of viable tissue beneath the burn eschar with or without subsequent vascular bacterial dissemination. Proliferation of subeschar bacteria was finally controlled, and death, due to pseudomonas burn wound sepsis, was significantly decreased by the topical application of Sulfamylon as advocated by Moncrief[3] and Lindberg.[2]

After 5 years of satisfactory experience with the use of opical Sulfamylon in the therapy of major burns, the mortality rate of patients with 30–60% total body surface burns has significantly decreased. This is closely associated with an increased incidence of pneumonia followed by bacteremia. Most of the pulmonary infections appeared to be primary, *i.e.* air borne, in origin, in contrast to the hematogenous pneumonia frequently associated with pseudomonas burn wound sepsis. Because topical therapy with Sulfamylon effectively prevents uncontrolled proliferation of the burn wound flora, it was the purpose of this retrospective study to review the bacterial culture data obtained during the past 4 years, in an attempt to identify an organism and a route of infection that might explain the increased mortality rate in previously salvageable burn patients. The recovery of *Providencia stuartii*, a member of the Enterobacteriaceae was found to have markedly increased in cultured blood, sputum, and urine, and positive cultures of Providence in both ante and post-mortem specimens were associated with a surprisingly high mortality rate in patients with pneumonia.

Methods

Retrospective analysis of 10,397 blood, sputum, and urine cultures obtained from 1,404 patients hospitalized with major burns at the U.S. Army Institute of Surgical Research during a 4-year period (1967–1970) form the basis of this report. In addition, burn wound surface cul-

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tures collected at the time of admission to the Institute from 902 patients during the same 4-year period were reviewed. Antibiotic sensitivity data available from 718 bacterial strains isolated from 457 patients admitted during the last 2 years of the study period were carefully evaluated. Finally, an analysis of detailed post-mortem data as well as post-mortem lung, burn wound, and blood cultures obtained from 70 patients who died in 1970 permitted closer scrutiny of the recent bacteriologic and pathologic alterations which resulted in death of the patient.

All clinical specimens were cultured as previously described by Lindberg.[1] Gram negative strains were differentiated by standard biochemical reactions in culture media and antibiotic sensitivity was determined by standard tube dilution tests which assay the minimum inhibitory concentration (MIC) of the test drugs in trypticase soy broth. Gram negative organisms were tested against tetracycline, Chloromycetin, Kantrex, cephalothin, colistimethate sodium, and Garamycin while the antibiotic battery utilized for gram positive bacteria included Kantrex, lincomycin, oxacillin, methacillin, tetracycline, Garamycin, and nafcillin. Inhibitory levels of 12.5 μg./ml. or less for gram negative and 6.25 μg./ml. for gram positive cocci are required for clinical effectiveness.

Culture specimens were aseptically obtained by experienced technicians. Surface cultures were collected from new patients admitted, a procedure which assures constant surveillance of the bacterial population being introduced to the clinic. Other clinical specimens were collected when clinical infection was suspected.

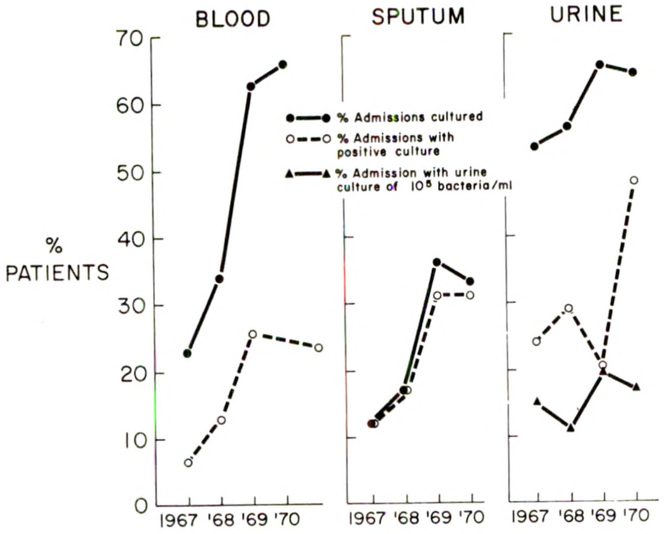

FIG. 1. Per cent of burn admissions from whom blood, sputum and urine cultures were obtained between 1967 and 1970 and the per cent of admissions in whom these cultures were positive. Note marked increase in incidence of positive blood and sputum cultures in 1969 and 1970.

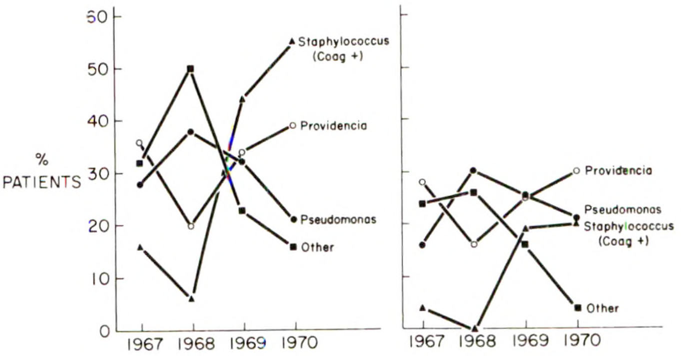

FIG. 2. On the left the incidence of patient bacteremia with specific organisms between 1967 and 1970 is depicted. In 1970, Providence bacteremia was almost twice as frequent as Pseudomonas bacteremia. On the right the incidence of specific organisms in patients with positive blood cultures who eventually died with bacteremia is depicted. *Providencia stuartii* was the most frequent fatal blood stream pathogen in 1970.

Results

Blood Cultures. As can be seen in Figure 1, the percentage of patients admitted to the Institute who had blood specimens taken for culture increased by almost 200% between 1967 and 1970 as the responsible physicians became aware of a new increase in incidence of bacteremia in the burn population. During the same period of time the incidence of positive blood cultures also tripled, thus justifying physician concern.

In Figure 2 the change in incidence of bacteremia with specific organisms in patients between 1967 and 1970 is graphically illustrated. A startling increase of 900% in the frequency of *Staphylococcus aureus* (coagulase positive) septicemia between 1968 and 1970 is immediately evident. In addition, it was surprising to note that the incidence of *Providencia stuartii* bacteremia was almost twice that of *Pseudomonas aeruginosa* in 1970. Moreover, this burned population appeared to show a rising incidence of Staphylococcal and Providence sepsis with a simultaneous decrease in Pseudomonas bacteremia.

If the percentage of all patients with positive blood cultures who eventually died with bacteremia is calculated (Fig. 2), a very different pattern emerges. *Providencia stuartii* assumes great importance as the most frequent fatal blood stream pathogen in the 1970 burn population supplanting the historically, more prominent role of *Pseudomonas aeruginosa*. On the other hand, Staphylococcal bacteremia, though increasing once again in pathogenicity, does not appear to be associated with the high incidence of burn mortality which is characteristic of the gram negative organisms, perhaps due to the effectiveness of antistaphylococcal agents.

The decreased mortality associated with *Staphylococcus aureus* (coagulase positive) in this population is confirmed in Table 1 in which absolute mortality rates associated with blood stream infection during the 4-year study period are calculated. Between 75 and 80% of all patients with Providence or Pseudomonas bacteremia died as compared to 37.2% of those patients with Staphylococcal septicemia. In those patients with clinical signs of sepsis prompting culture of blood, but in whom no bacterial growth could be demonstrated, the death rate was only 13.2%.

Sputum Cultures. More frequent evaluation of pulmonary bacterial growth by sputum culture was also noted during the last 2 years of the study (Fig. 1). The incidence of positive findings in patients so cultured remained high (> 85%) reflecting an increased frequency of pneumonitis in 1969 and 1970.

In Figure 3 a marked increase (700%) in *Providencia stuartii* recovery from sputum culture during the 4-year study period is depicted. A very heterogeneous group of organisms including *Escherichia coli,* Proteus, Staphylococcus, Streptococcus, Candida, Mima, Serratia, Citrobacter, and Hafnia were found most frequently in sputum cultures, although no single species was recovered from more than 10% of cultures. Between 1967 and 1970 there was a moderate decrease in the isolation of these organisms and their incidence followed a reciprocal relationship with that of the Providence group. No significant change in the attack rate of Pseudomonas could be demonstrated.

Figure 3 also illustrates the percentage of all positive sputum cultures which were isolated from patients who later died. Again the striking increase in Providence infections (> 700%) during the study period is apparent and its incidence in dying patients parallels its frequency of appearance in all patients with positive sputum cultures, indicating a relatively high and constant association with death. On the other hand, the heterogeneous group of bacteria isolated is clearly less significant, if death is selected as the critical end point.

The absolute mortality rates in patients with positive sputum cultures are summarized in Table 2. Death resulted in 61.8% of patients with Providence as compared to mortality rates of 51.9% with Pseudomonas, 47.2% with Aerobacter, and 43.6% with the heterogenous, less frequently isolated bacterial species.

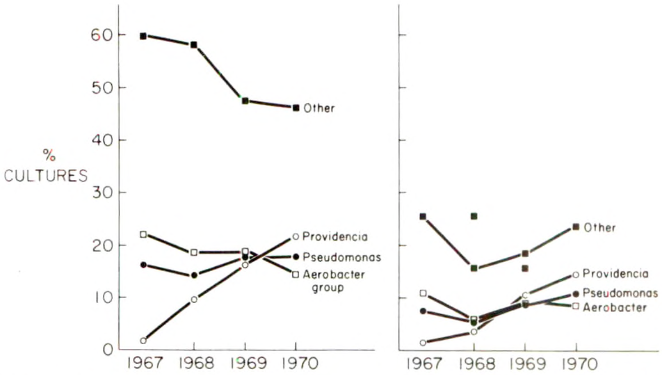

FIG. 3. Incidence of organisms recovered from all patients with positive sputum cultures is illustrated on the left, revealing a marked increase in the recovery of Providence from sputum. On the right, the incidence of bacterial species recovered from sputum of patients who later died is graphically displayed.

Urine Cultures. Urine specimens for culture have routinely been collected from a large percentage of patients (Fig. 1) at this institution, since urethral catheterization for accurate urinary output measurements is critical to successful resuscitation of patients with major thermal injuries, and the presence of this foreign body within the lower urinary tract would appear to favor the development of infection. Approximately 20–30% of patients admitted yielded organisms on culture each year until 1970 when the incidence unexpectedly increased to 48%. However, there was no concomitant increase in serious urinary tract infections, as indicated by quantitative culture of greater than 10^5 organisms per milliliter of urine, and only 10–20% of patients each year ever demonstrated these higher concentrations of urinary microorganisms.

Cultures of urine showed a large increase in the incidence of Candida urinary tract infections between 1968 and 1970 (Fig. 4). More than one-third of urine cultures in 1970 yielded either Providence or Candida isolates. In contrast the incidence of *E. coli,* Pseudomonas, and Proteus isolates has markedly decreased during the study period. If only clinically significant urinary tract infections, as defined by quantitative cultures showing more than 10^5 bacteria per milliliter of urine were analyzed (Fig. 4), essentially the same distribution of isolated microorganisms was seen.

Surface Cultures at Time of Admission to Hospital. It has been the practice of this Institute during the past 10 years to obtain surface cultures from the burn wound at the time of admission to the hospital. This allows con-

TABLE 1. *Mortality Rate Associated with Positive Blood Culture*

Organism	Mortality Rate
Pseudomonas aeruginosa	80.6%
Providencia stuartii	76.0%
Staphylococcus aureus (Coag.+)	37.3%
Others	54.0%
Negative Blood Cultures	13.2%

TABLE 2. *Mortality Rate Associated with Positive Sputum Culture*

Organism	Mortality Rate
Providencia stuartii	61.8%
Pseudomonas aeruginosa	51.9%
Aerobacter Group	47.2%
All Other	43.6%

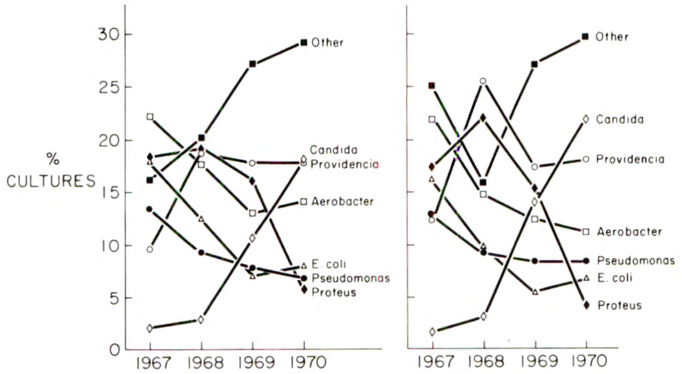

FIG. 4. Urine culture analysis revealed a striking increase in the incidence of Candida between 1968 and 1970 regardless of whether all microbiological growth in urine was considered (left) or only positive cultures with greater than 10^5 organisms per ml. were considered (right). Note also the high incidence of Providence urinary tract infection.

stant surveillance of the bacterial population being introduced into the local environment. At the same time this procedure provides an internal control of cultures obtained during hospitalization, in that major increases in the incidence of isolation of a particular species of organism can be compared with the incidence of recovery of that same species from burns in patients of similar age arriving from other hospital environments. The incidence of recovery of *Providencia stuartii* from burn surface cultures at the time of admission to this Institute is shown in Figure 5. Prior to the sixth postburn day the organism is infrequently isolated. However, at all time intervals thereafter there has been a dramatic increase in the incidence of burn wound colonization with Providencia between 1967 and 1970, all of which occurred prior to exposure to the local bacterial environment of the Institute. These findings support the contention that the increased number of Providence infections during the past 2 years has not resulted from a local contaminating source, but rather represent a widespread increase in the environmental occurrence of this organism.

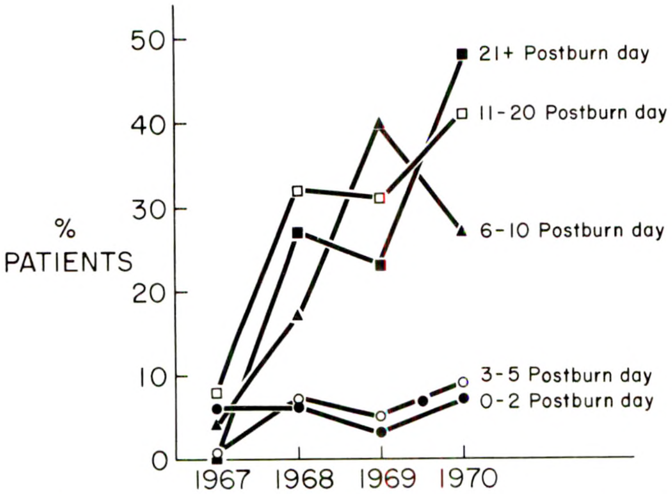

FIG. 5. Per cent of patients with admission surface cultures that were positive for *Providencia stuartii*. All cultures were obtained prior to exposure to the institute's clinical care center, and thus, are representative of the burn flora acquired at other referring hospitals.

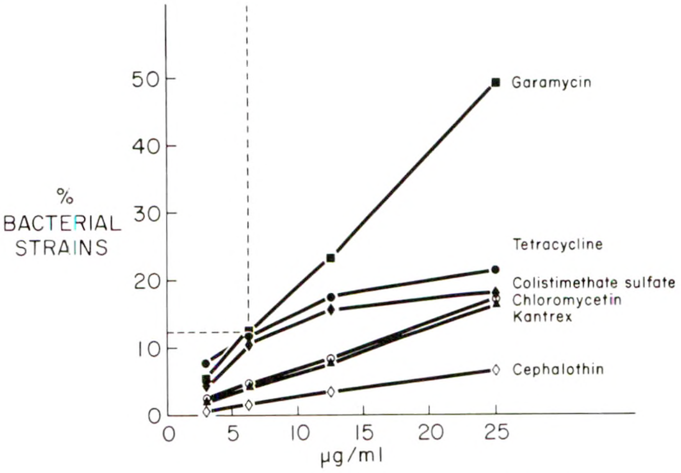

FIG. 6. Per cent of *Providencia stuartii* stains inhibited by ascending concentrations of various antibiotics. Only 12% of isolates were inhibited by any single drug at 6.25μg./ml., the highest plasma concentration which is consistently achieved.

Antibiotic Sensitivity. The percentage of *Providencia stuartii* strains isolated in 1969 and 1970, which were sensitive to ascending concentrations of various antibiotics is indicated in Figure 6. Each level inhibited all strains inhibited at lower levels. At 6.25 μg./ml., the highest plasma concentration which is consistently achieved with safety, the two most effective antibiotics, namely Garamycin and tetracycline, inhibited only 12% of the isolated strains of *Providencia stuartii*.

Mortality. Interpretation of the mortality rates of burned patients admitted to the Institute is difficult since there may be considerable delay in admission of patients injured outside the continental United States while arrangements for inter-continental air evacuation are made. As a result death following admission is rare in this group because more severely injured patients with significant complications often die without ever attaining a clinical condition deemed satisfactory to withstand a 12–20 hour flight to the United States. Therefore, the mortality data in Table 3 and Table 4 have been restricted to all patients admitted from within the continental United States during the study period. Since age of the patient significantly affects predicted mortality rates, the figures presented pertain only to the young adult group (ages 15–45) with the best chance of survival. Predicted mortality rates are estimated from probit analysis of survival data at the Institute between 1964 and 1967.

TABLE 3. *Body Surface Involvement, Mortality and Predicted Mortality of Patients (Ages 15–45)*

	1968			1969			1970		
% Burn	No.	Deaths	Predicted Deaths	No.	Deaths	Predicted Deaths	No.	Deaths	Predicted Deaths
0–30	37	1	0	28	0	0	30	2	0
30–60	22	4	4.8	27	12	4.0	36	15	5.8
60–100	11	7	8.8	26	22	20.7	16	16	12.8
Total	70	12	13.6	81	34	25.6	82	33	18.6

There has been a marked increase in the rate of absolute mortality as compared to predicted mortality rates between 1968 and the 2-year period from 1969 through 1970 (Table 3 and Table 4). It is clearly evident that the elevated death rate has occurred primarily in the 30–60% total body surface burn group.

The above observations prompted a detailed re-examination of all autopsy findings of patients who died n 1970. Pneumonia was found to be a significant cause of death in 45 of the 70 deaths (64.3%). *Providencia stuartii* was isolated from postmortem lung cultures in 29 of these 45 patients (64.4%).

Discussion

The frequency with which *Providencia stuartii* was solated from blood, sputum, urine, and the burn wound cultures of thermally injured patients was unexpected prior to this retrospective analysis. Moreover, the marked rise in the incidence of Providence infection in sputum cultures is alarming, particularly in view of the apparent ncrease in pulmonary deaths among the 30–60% total body surface burn group, a patient population which heretofore has enjoyed the greatest benefits from treatment with topical chemotherapy. These results conclusively indicate that *Providencia stuartii* infection was associated with subsequent death more often than *Pseudomonas aeruginosa* during the past 2 years and that the ethality of this organism is probably of the same magniude as the better recognized Pseudomonas.

Monitoring of the environment for bacteriologic reservoirs is performed routinely at the Institute. In addition, xhaustive bacteriologic surveys of the water supply, air onditioning systems, hydrotherapy tanks, medical and nursing personnel, and pulmonary inhalation equipment have been accomplished several times during the study period. At no time has a local source of Providencia infecion been discovered. The fact that there has been a marked rise in *Providencia stuartii* colonization of the burn wound at admission (Fig. 5), prior to exposure to he local environment, strongly supports the suspicion hat this organism is occurring with greater frequency throughout the hospital environment in the United tates. Because its identification depends on careful biochemical testing in a number of different types of culture media, in practice it is often left undifferentiated from the other members of the Enterobacteraciae group and not infrequently hospital laboratories simply report these organisms as "Enterobacter group," paracolon bacillus," "proteus," or "unidentified gram negative bacteria." However, the emerging importance of this microorganism in clinical septicemia has been suggested by others.[5,7]

TABLE 4. *Absolute and Predicted Mortality (Age 15–45)*

Year	Mortality Rate	Predicted Mortality Rate
1968	17.1%	19.4%
1969	42.0%	32.0%
1970	40.2%	22.7%

Antibiotic therapy has been disappointing as evidenced by the poor survival rate following pulmonary or blood stream infection. *In vitro* susceptibility to presently available antibiotics at clinically attainable concentrations was demonstrated in less than 15% of the isolates. Somewhat better *in vitro* results with Kantrex and Garamycin were reported by Washington and associates[7,8] although these authors tested only 20 isolates from the Providence group.

This retrospective analysis of infection in a large burned patient population suggests the emergence of a highly lethal and relatively resistant bacteria in the form of *Providencia stuartii.* It appears to attack primarily via the respiratory tract. The precise pathophysiology of this infection awaits the development of a suitable animal model.

Summary

During the past 2 years mortality among patients with 30–60% total body surface burns has significantly increased. These deaths have been associated with a rising incidence of *Providencia stuartii* sepsis along with more frequent clinical and postmortem findings of pneumonia. Providence pneumonia and bacteremia have occurred with greater frequency than similar infections with *Pseudomonas aeruginosa* and appears to be equally as lethal in the burned patient. Surface cultures from the burn surface on admission strongly suggest that there is a widespread geographical distribution of this organism within the United States which has remained largely unrecognized, perhaps as a result of the time-consuming and relatively expensive laboratory procedures required to differentiate Providence from other members of Enterobacteraciae. Unfortunately, the current available antibiotics, which are most often utilized to combat gram negative bacterial infection, have been ineffective in inhibiting more than 85% of the isolated strains of *Providencia stuartii.*

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Cell-Mediated Immunity after Thermal Injury

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THE IMMUNOLOGICAL changes following burns have received considerable attention in the recent literature. It has been generally accepted that (1) Serum immunoglobulins become depleted in the postburn period,[3,13] (2) Skin allograft rejection is delayed in proportion to burn size,[5,14] and (3) Burn patients and animals become anergic to certain tests of delayed cutaneous hypersensitivity.[4,15] Other evidence on the immunological status of the burned host is more controversial. For example, the humoral response to systemically introduced antigens seems adequate[1] and the response of burn lymphocytes to phytohemagglutinin stimulation is in fact increased.[6,10]

In the combined clinical and laboratory study to be presented, we have attempted to look at some further aspects of cell-mediated immunity in burns. Specifically, we investigated the fate of internal as opposed to cutaneous allografts following burns; the primary and anamnestic responses to cutaneous allergens; the ability of burn lymphocytes to recognize foreign histocompatibility antigens; and the possible presence of any serum-transferable factor which might mediate a depression of cell-mediated immunity *in vitro.*

Materials and Methods

Rejection of Internal Allografts in the Burned Rat. Adult Lewis and (Lew × BN) F_1 hybrid rats were used throughout. A 30% total body burn was inflicted on the recipient rat according to a previously described method, using a standard 10-second immersion scald burn;[17] then, following varying intervals of time, operation was performed according to a modification of the method of Wheeler.[18] Recipient animals were anesthetized and the left kidney exposed through a subcostal incision. A fine slice of tissue was removed from the cortex of the kidney and, following cessation of bleeding, a slice of the spleen of the donor animal was implanted on to the host kidney surface and allowed to adhere without sutures. The kidney bearing the graft was then carefully replaced in the abdominal cavity and the abdomen closed in layers. All animals were sacrificed at 10 days and the spleen slice grafts scored grossly for color, size and vascularity. The kidneys were then excised, examined histologically (with the examiner having no knowledge of the specimen source), and scored by light microscopy for residual splenic architecture, lymphoid follicles, vascularization, necrosis and fibrosis. Using these criteria, a scoring system was devised from 0 (complete necrosis or fibrosis) to 6 (perfect survival), and this method was used to describe the state of the graft at 10 days. Figure 1 illustrates the histologic appearances of these spleen slice grafts at 10 days. The experimental design is detailed in Table 1. It will be noted that the principal experimental group (Group II) is so designed that a pure host-versus-graft reaction must take place. This was done in order to eliminate histological confusion by the occurrence of a bidirectional reaction.

A separate group of Lewis rats (n = 10 per group) received skin allografts from (Lew × BN) F_1 donors to establish skin rejection times for this particular strain. Recipients were inflicted a 15% scald burn placed as far posteriorly as possible on the back, then a 2 × 2 cm. partial thickness skin graft was placed on a surgically

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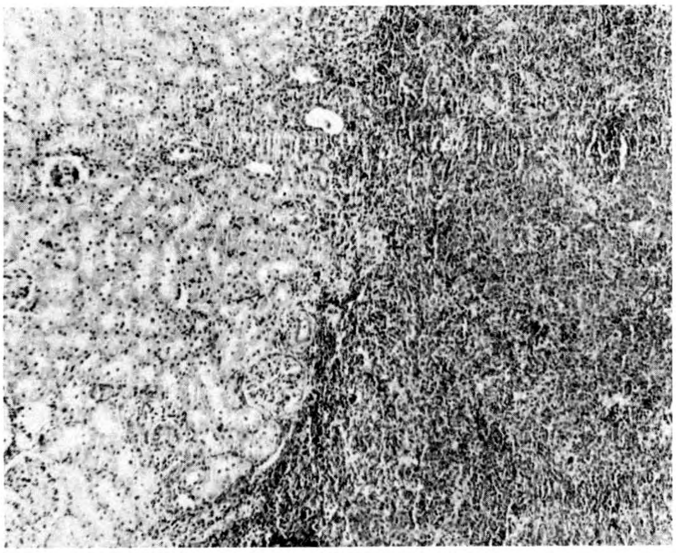

FIG. 1A. Compatible spleen slice graft (right) on renal cortex (left). Note cellularity of spleen and normal follicular architecture.

TABLE 1. *Experimental Design for Spleen Slice Allografts [F_1 refers to (Lewis × BN)F_1]*

Group I—Compatible Grafts	Group II—Incompatible Grafts
Lewis → F_1	F_1 → Lewis
F_1 → F_1	F_1 → Lewis with burn 10 days pregraft
Lewis → Lewis	F_1 → Lewis with burn 4 days pregraft
F_1 → F_1 with 30% TBS burn 4 days pregraft	F_1 → Lewis with burn 1 day pregraft
Lewis → Lewis with 30% TBS burn 4 days pregraft	

prepared bed anterior to the burn, and sutured in place. Control rats received skin grafts only. All grafts were read daily for signs of rejection, and the day of necrosis of 50% of the graft was taken as the day of rejection.

Skin Tests in Burned Patients. Eight patients, with burns ranging from 18 to 85% of the total body surface, were subjected to skin testing as follows. On admission, the inflammatory reaction was assessed by a skin-window technic, in which a small area of unburned skin was abraided with a scalpel, and a microscope coverslip secured over the area. Twenty-four hours later the coverslip was removed, fixed, and stained, and polymorphonuclear leucocytes and eosinophils counted. Results were classified as positive or negative. These patients were simultaneously tested with an intracutaneous injection of Monilia antigen, Trichomonas antigen, and Streptokinase-Streptodornase antigen. Since these tests are negative in persons with no prior exposure, a negative result provided no information. We retested all the patients at 2 weeks. The tests themselves do not induce a state of delayed hypersensitivity to the antigen, therefore a conversion from negative at first testing to positive at second testing can be interpreted as a transient loss of cell-mediated immunological memory to these antigens. Finally, all patients were sensitized on admission to Dinitrofluobenzene. This substance, in contrast to the previous group, does produce sensitization. Patients were challenged with DNFB again at 2 weeks. Failure to react to the challenge dose was interpreted as abolition of the primary immune response during the postburn period.

Recognition of Heterologous Histocompatibility Antigen by Human Burn Lymphocytes. We used a modification of the rat popliteal node assay.[7] The assay was originally designed to test the ability of parental rat lymphocytes, when injected into the hind footpad of the F_1 hybrid, to produce a Graft-versus-Host reaction in the draining popliteal lymph node. In this setting, we have already described a severe depression of the ability of spleen cells from injured rats to induce the reaction.[12] In the present experiments, 20 ml. of peripheral blood was obtained from the patients in the study at various intervals postburn. Leucocytes were separated by sedimentation, then 10^6 cells in 0.5 ml. medium were injected into the hind footpad of Lewis rats. One week later, the nodes were excised and processed for thymidine incorporation. Full details of the method are given elsewhere.[12] Results were expressed as the tritiated thymidine incorporation per minute by the rat popliteal node.

Ability of Burn Serum to Depress in vitro Lymphocyte Transformation. Peripheral lymphocytes were obtained from normal human volunteers, separated by dextran sedimentation, and adjusted to a final concentration of 10^6/ml. Triplicate tubes were cultured for 6 days in a CO_2 ambient, in the presence of: (i) no additives, (ii) Monilia antigen 1:1000, 0.1 cc/culture tube, (iii) Monilia antigen with normal serum 0.1 cc, (iv) Monilia antigen with burn serum from our patients, 0.1 cc of undi-

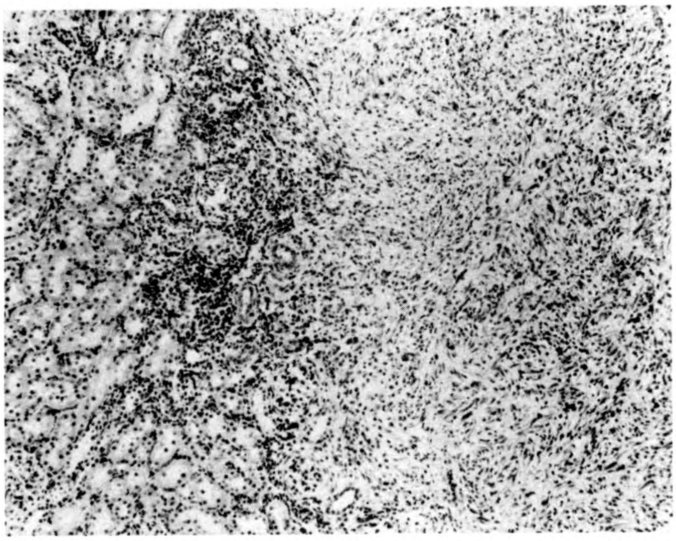

FIG. 1B. Incompatible spleen slice graft (right) on renal cortex (left). The spleen is avascular and infiltrated with fibrous tissue.

luted serum and also 1:1, 1:2 and 1:4 dilutions. After 6 days, cultures were tagged with C_{14} thymidine and harvested. Since the reaction of peripheral lymphocytes to Monilia antigen depends on prior exposure, rather than expressing our results in absolute figures (disintegrations per minute), we expressed them as the mitotic index, 100% being the uptake of thymidine by the cultures containing Monilia antigen only. In this way, variations of reactivity due to differing states of sensitization of the lymphocyte donors was eliminated, and each series of cultures compared only to the activity of lymphocytes from the same donor sample.

Aliquots of serum from burned patients used in these experiments were set aside for serum cortisol determination. The serum cortisol concentration was compared with the percent inhibition produced in the Monilia-stimulated cell cultures by the same samples of serum.

Results

Rejection of Internal Allografts in the Burned Rat. The results are listed in Table 2. The mean group scores for immunologically compatible groups, with or without thermal injury, range from 4.2 to 5.4, that is, good survival. Although none of these grafts reached the perfect score of 6, it is known that spleen slice grafts do not reach optimal follicular reorganization for 3 to 4 weeks using this technic,[18] and all our grafts were inspected at 10 days. The mean score of the incompatible groups ranged from 1.6 to 2.2 showing the severe rejection that would be expected from these Ag/B incompatible animals. Statistical comparison by analysis of variance of the scores of compatible groups is significant at the 0.1% level. The incompatible groups of rats with no thermal injury showed no significant difference in rejection from the incompatible groups grafted at 1, 4 or 10 days postburn ($p > 0.5$). Thermal injury in this model, therefore, failed to depress the rejection reaction. By contrast, the skin allograft survival in burned rats of the same species was prolonged from a control value of 6.4 ± 0.3 days to 8.6 ± 0.7 days ($p < 0.01$). This prolongation is small, but the burn inflicted on the recipient rats was only 15% of the body surface; the finding is therefore in accord with previous reports of increased skin graft survival following burning.

TABLE 2. *Rejection of Spleen Slice Grafts Following a 30% Burn (F_1 = (Lewis × BN)F_1)*

Donor	Recipient	n	No. of Days Burned Before Grafting	Mean Score*
F_1	Lewis	6	No burn	1.6
F_1	Lewis	5	10	2.2
F_1	Lewis	6	4	2.0
F_1	Lewis	8	1	1.6
Lewis	F_1	5	No burn	5.0
F_1	F_1	5	No burn	5.4
F_1	F_1	6	4	4.7
Lewis	Lewis	6	No burn	4.2
Lewis	Lewis	6	4	4.2

* Perfect survival = 6; complete rejection = 0

Analysis of variance: Within group differences for Group 1, $p > 0.5$
Within group differences for Group II, $p > 0.5$
Group 1 vs. Group II, $p < 0.001$***

Skin Tests in Burned Patients. Of the eight patients tested, one with 85% burns survived long enough to allow initial testing only. Results are shown in Figure 2. It can be seen that two patients with burns of 18% and 20% respectively showed no diminution in their cutaneous responses at all. Two patients with 24% and 30% burns had a negative initial response to some of their immunological memory tests which turned positive at the second testing. Patients with 31, 38 and 52% burns remained negative to all skin tests. Although it is possible that all three patients had no prior contact with any of the three antigens used, in a military population this is extremely unlikely. The same three patients also failed to sensitize to dinitrofluobenzene, indicating an abolition of the primary cell-mediated immune response. The patient with 85% burns was negative to all tests and showed no inflammatory response by the skin window method.

In these patients therefore, normal inflammatory and immunological responses were noted at a burn size of 20% or less. As the burn size increased, immunological memory to a cell-mediated antigenic stimulus, the ability to respond to a primary cell-mediated antigen, and finally, the inflammatory reaction, were progressively abolished.

BURN SIZE %	ON ADMISSION				AT 2 WEEKS			
	Rebuck	SDSK	TRICHO	MONI	DNFB	SDSK	TRICHO	MONI
18	+	+	+	+	+	+	+	+
20	+	+	+	−	+	+	+	−
24	+	−	−	−	+	+	+	−
30	+	−	−	−	+	+	−	+
31	+	−	−	−	−	−	−	−
38	+	−	−	−	−	−	−	−
52	+	−	−	−	−	−	−	−
85	−	−	−	−				

FIG. 2. Skin tests following burns.

Recognition of Heterologous Histocompatibility Antigen by Human Burn Lymphocytes. Results are shown in Figure 3. The rat popliteal node reaction was normal in patients with 18, 20, 24, and 30% burns. In the larger burns, it was severely depressed for up to 1 week postburn, recovering to normal levels by two weeks. Since the reaction here was two-way, there having been no mitamycin-treatment or radiation of either human or rat

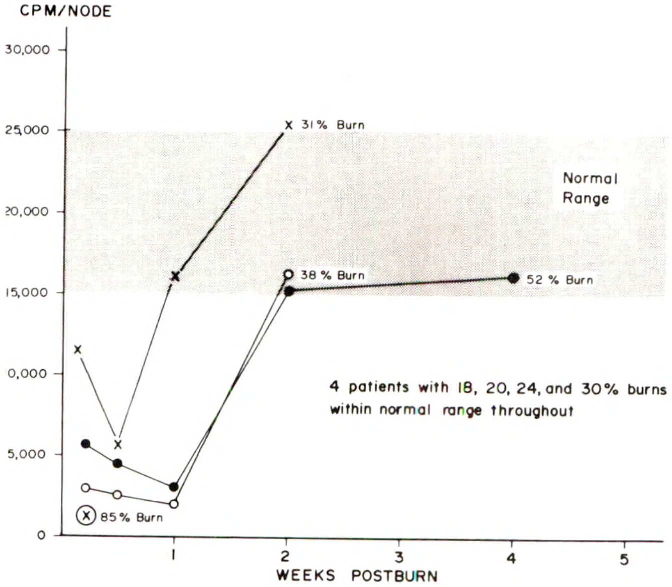

FIG. 3. Popliteal node assay.

cells, these results strictly speaking cannot be interpreted as a failure of the human cells to react. However, there is evidence in the literature[5] that the histocompatibility markers of lymphocytes are not altered by thermal injury and presumably the rat cells should react to the human lymphocytes. In this case, one may conclude that the depression in the reaction as noted in our experiments was a reflection of the inability of the burned human cells to react against the histocompatibility antigens of the rat at least until one-way mixed lymphocyte reactions are investigated. This would agree well with other recent observations describing a suppression of the T-lymphocyte population postburn over the same time period.[9,12]

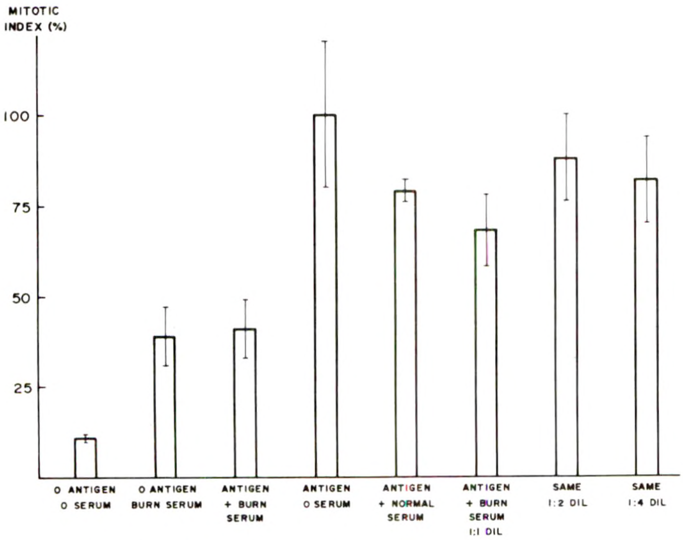

FIG. 4. Results of stimulation with Candida antigen.

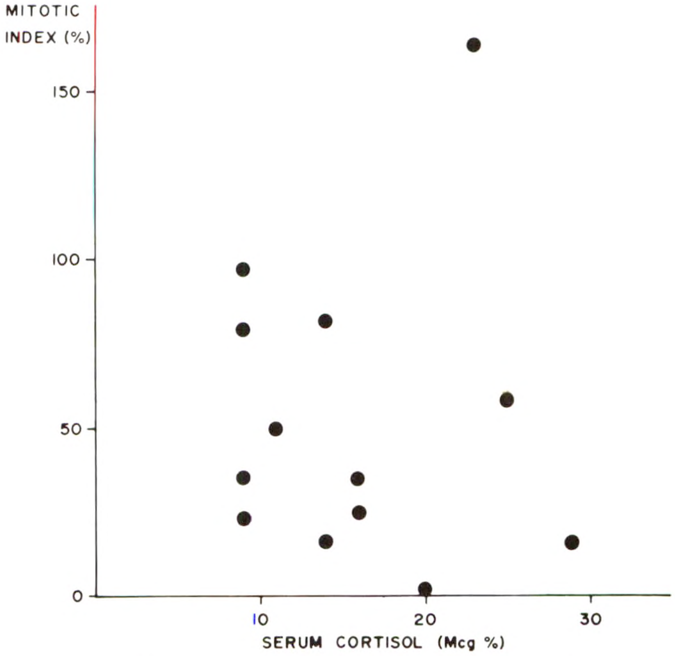

FIG. 5. Serum cortisol and inhibition of mitogenesis.

Ability of Burn Serum to Depress in vitro Lymphocyte Transformation. Results are shown in Figure 4. Taking the thymidine incorporation per minute of cultures of normal lymphocytes stimulated by Monilia, without serum, as 100% (actual count 1751 ± 393), the following findings were noted. The addition of normal serum had no statistically significant effect on Monilia-stimulated cultures. The addition of undiluted burn serum reduced blast transformation to 41% ± 7.9 ($p < 0.01$). The addition of a 1:1 dilution of burn serum produced a lesser depression at 68% ± 10.4 ($p < 0.05$). Further dilution of the burn serum to 1:2 and 1:4 abolished the effect. Spontaneous transformation (no antigen and no serum added) was 11% ± 1.2.

Serum cortisol values on the samples ranged from 9 to 23 mg./100 ml. A comparison of the per cent depression produced by the serum on Monilia-stimulated blast transformation with the serum cortisol concentration of the same sample is shown in Figure 5. Although the numbers are small, there appears to be no correlation between the degree of inhibition of mitogenesis and serum cortisol levels, and no correlation can be found by statistical analysis. Similarly, we were unable to document a correlation between burn size and the degree of inhibition of mitogenesis.

Discussion

Our findings of depression of cell-mediated immunity as indicated by abolition of certain delayed cutaneous hypersensitivity reactions are in agreement with previous reports.[4,15] It is interesting that the activation of the clone of immunologically responsive cells which are responsible for immunological memory appears to be depressed by a smaller burn than is necessary to depress the primary reaction. This is in contrast with the response of humoral immunity, in which the secondary response is normal or even exaggerated postburn.[2] The relationship between burn size and the degree of depression of cell-mediated immunity, noted in the past,[5] is confirmed by our findings in the popliteal node assay.

The apparent normality of internal allograft rejection in the face of the above information is intriguing, but can probably be explained on a time-related basis. Since the time of sacrifice of our rats for scoring the spleen slice grafts was always 10 days, and the earliest grafts were placed one day postburn, these grafts had a minimum of 11 days in which to undergo rejection. In the rat, the ability of burn spleen cells to induce a Graft-versus-Host reaction is profoundly impaired immediately postburn, but recovers rapidly by 4 to 7 days.[12] This rapid recovery of T-cell function could allow enough time for histological rejection to occur by the 11th day. Skin allograft rejection in major burns, by contrast, is prolonged for a considerable time, sometimes weeks.[2,5] Two alternative explanations for this finding may be offered. First, antigenic processing from the skin may be less efficient than from a well-vascularized internal organ, and second, an organ-specific factor may be liberated from burned skin which depresses skin graft rejection. In the unburned dog, kidney grafts are more rapidly rejected than skin grafts.[11] Furthermore, a free F $(ab')_2$ fragment of immunoglobulin G has been isolated from the serum of burned patients.[8] Since this complement-independent serum fraction has an enhancing effect on organ allograft survival,[16] it is possible that the prolongation of skin allografts in burns is in the nature of an immunological enhancement.

We have demonstrated severe depression of *in vitro* lymphocyte transformation by a serum-transferable factor which, at least in our small series, does not appear to be cortisol. If this factor were of biological importance, one might expect a correlation between burn size and the degree of depression, a correlation which we were not able to demonstrate. We did not differentiate between second and third degree burns in this series, and it is possible that the depth of tissue destruction is of relevance in determining the release of the serum factor. Until further investigations are carried out, the implications of such a serum factor must of necessity be conjectural.

Summary

A study of cell-mediated immunity on eight burn patients and groups of inbred rats has shown that immunological responses remain normal in burns smaller than 20% body surface. As the burn size increases, immunological memory and the primary cellular response become progressively abolished. In contrast to skin allograft rejection which is delayed by thermal injury, internal organ rejection proceeds normally. It is hypothesized that an organ-specific factor, possibly an enhancing antibody, may be released from burned tissue. There is a serum-transferable factor present in burn patients which is capable of depressing the *in vitro* blast transformation of stimulated, normal human lymphocytes. Although this factor does not appear to be cortisol, its biological importance at present remains unclear.

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The Effect of Human Amniotic Membranes on the Bacterial Population of Infected Rat Burns

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THE *sine qua non* of healing for the burn wound is the reestablishment of continuity of the skin. This may occur spontaneously in partial-thickness burns, or by the successful application of autografts in full-thickness burns. The non-uniformity of the thermal injury usually requires that both of these modalities be utilized in patients with major burns. Although the recent introduction of topical antibacterials has allowed a greater percentage of burns to proceed to healing without grafting, the need for wound closure by autografts remains. In a 50 per cent full thickness burn in an adult, the amount of skin required to obtain wound closure has been estimated at 6,000 square centimeters.[29] Because this large amount of donor area is not always immediately available on the patient, other substances have been sought to obtain a temporary closure of the wound, while awaiting the time when donor areas may be used again.

Over 100 years ago, Pollock applied the first homograft onto a burned patient.[14] Ten years later Lee attempted the first heterografting of burn wounds in the United States.[17] Later, Ivanova suggested that fetal skin might have an advantage over adult skin when used as a homograft on burned patients because the infantile tissue possessed more "energetic vitality."[15] Following the suggestion of W. L. Thornton, a senior medical student at The Johns Hopkins University, John Staige Davis in 1910 reported attempts at grafting pieces of the lining of the amniotic sac onto granulating wounds.[7] Sabella treated a burned patient with amniotic membranes for the first time on June 16, 1912.[25]

Early attempts at using these substitutes for the patient's own skin were designed to obtain epithelial continuity of the burn wound and to provide permanent coverage. Although Davis[8] stated, in 1919, that these substitutes, if left in place would eventually be rejected; attempts at permanent replacement continued. By 1938, Bettman[2] had reviewed all of these attempts and reported that substitute coverage could be gained while they were in place. The concept of homograft split-thickness skin being used as a temporary emergency biological dressing was popularized by Brown and associates.[3,4] Douglas[10] reported using amniotic membrane tissue as such a temporary covering for burns, later, however, to be replaced by split-thickness skin autografts.

Temporary biological dressings have a demonstrated usefulness in rendering the burn wound less painful, in decreasing the fluid and protein loss from the burn surface, and in gaining valuable time for allowing donor areas to re-epithelialize prior to the next harvesting of autografts. All of the biological dressings mentioned can serve these functions. In addition, Eade[12] has shown that homografts, used as temporary dressings, were useful in decreasing the bacterial population in the granulating tissue of the burn wound. Switzer *et al.*, showed a similar effect with heterografts.[30]

The effect of amniotic membranes on the bacterial growth in the wound has not been previously reported. The purpose of this study was to re-evaluate the use of amniotic membranes as a temporary biological dressing both in the laboratory situation and in patients with thermal injuries.

Materials and Methods

Fresh amniotic membranes were obtained at the time of delivery from sero-negative mothers, who had no

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history of either premature rupture of the membranes or endometritis. The membranes were removed from the placenta aseptically, making no attempt to separate them into amnion or chorion. Using aseptic technic, the membranes were passed through five rises of sterile isotonic saline. In addition, those not being used immediately in the laboratory studies, were passed through one rinse of 0.025 per cent sodium hypochlorite and an additional five rinses of saline prior to being stored at 4° C for clinical use. All membranes were cultured at 24 hours, 3 days, 1 week, 2 weeks, 4 weeks and 6 weeks.

Part "A"

Fifty white, Sprague-Dawley rats weighing 200–250 Gm. underwent a standard 20% full-thickness scald burn of the back using the Brooke burn model. They were immediately topically inoculated with 10^8 *Pseudomonas aeruginosa* organisms obtained from fresh 18-hour broth culture. After 5 days, those rats surviving the burn wound sepsis, underwent burn escharectomy.

The area beneath the removed eschar was divided into three equal areas and tissue biopsies were obtained from each area for quantitative and qualitative bacterial analysis.[22] After cleansing the surface of the wound with isopropyl alcohol, a piece of tissue was removed. It was aseptically weighed, flamed, and homogenized after being diluted 1:10 with thioglycollate. Serial tube dilutions and backplating were then performed to arrive at a bacterial count. Following biopsy, the three areas of the burn were treated as follows: one had an amniotic membrane sutured into the defect; another had a piece of human skin approximately 0.014 inches in thickness sutured into the defect; and the third area was left untreated as a control (Fig. 1). The positions chosen for each type of treatment were randomized on the various rats. The amniotic membranes and skin grafts were replaced by fresh material every 48 hours. At the time of each change, tissue biopsies were obtained for quantitative and qualitative bacteriology.

Part "B"

A comparison of the *in vitro* effect of human split-thickness skin and amniotic membrane on bacterial growth was performed. Varying inoculums of 18-hour broth cultures of *Pseudomonas aeruginosa* and *Escherichia coli* were placed into plain thioglycollate and into thioglycollate containing a homogenate of either amniotic membrane or split-thickness human skin. The inoculums ranged from 10^3 to 10^8 organisms. The amount of skin or membrane used in the homogenate ranged from 50 mg. to 400 mg. (Fig. 2). The cultures were incubated at 37°C for 18–24 hours. Following incubation, serial tube dilutions and backplating were performed to obtain the number of bacteria present in each culture.

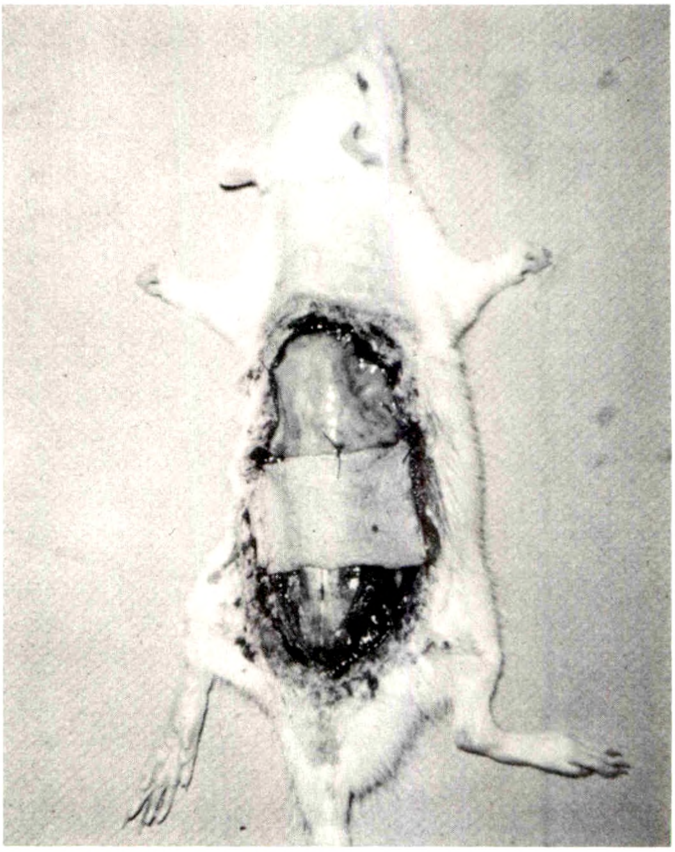

FIG. 1. Three areas of escharectomized infected burn treated with amniotic membrane, human split-thickness, or left untreated as a control.

Part "C"

Ten patients with deep partial-thickness or full-thickness burns were studied. The patients were treated with topical antibacterial agents until eschar separation in full-thickness injuries. The agents used were silver sulfadiazine (1%), sulfamylon acetate (10%), and gentamycin sulfate (0.1%). At that point, the topical ther-

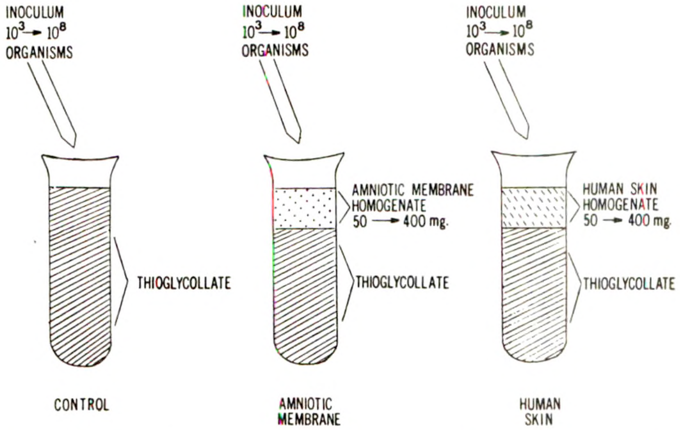

FIG. 2. Design of *In Vitro* experiment to test the effect of biological dressing homogenate on bacterial growth.

TABLE 1. *Effect of Amniotic Membranes and Human Skin on Bacterial Growth in Burned Rats.*

	Rats Surviving Infected 20% Burn					
	48 hours after treatment			96 hours after treatment		
Treatment Group	animals decreased count (%)	animals increased count (%)	animals no change (%)	animals decreased count (%)	animals increased count (%)	animals no change (%)
Control	18	50	32	40	20	40
Human Skin	29	50	21	90	0	10
Amniotic Membrane	58	13	29	100	0	0

apy was discontinued and the biological dressings begun. In the deep partial-thickness burns, topical antibacterials were used during the acute stage of burn edema. Prior to the initial application of amniotic membrane of homograft split-thickness skin, tissue biopsies were obtained for bacteriologic analyses. The biological dressings were left in place 48 hours and then replaced. At each change of the biological dressings, tissue biopsies were taken from the underlying bed. Biological dressings were used in full-thickness burns until replaced by autografts and in partial-thickness burns until re-epithelialization occurred.

Results

Culture of amniotic membranes prepared in sterile isotonic saline alone occasionally yielded positive cultures after storing. A single rinse of 0.025 per cent sodium hypochlorite was found to sterilize the membranes sufficiently, so that all cultures have remained negative throughout the 6-week period tested.

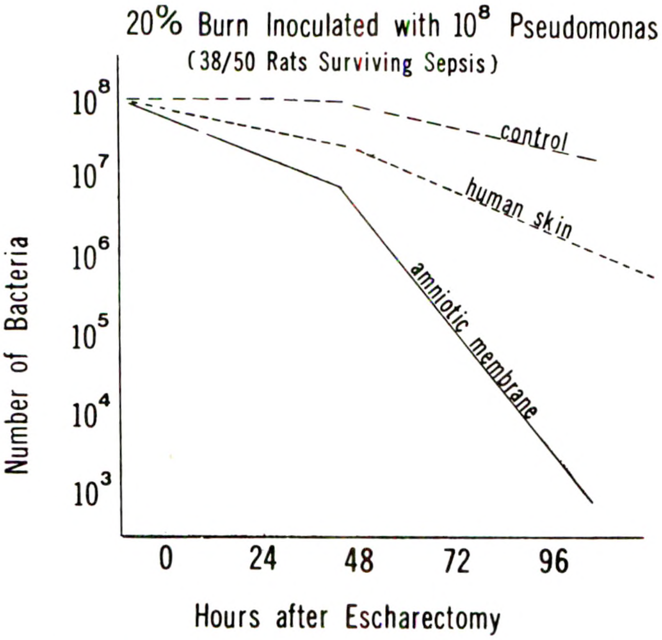

FIG. 3. Geometric means of bacterial counts in subeschar burn tissue versus time after initiation of treatment with biological dressings.

Part "A"

Fifty rats were initially burned and inoculated with 10^8 Pseudomonas organisms. Thirty-eight rats survived burned wound sepsis for 5 days. All three methods of treating the infected burn were effective in decreasing the bacterial count in the sub-eschar tissue. (Table 1). At 48 hours, escharectomy alone had decreased the bacterial count in 18 per cent of the animals. However, in 50 per cent of the animals the bacterial count in the control area had increased. The application of human skin decreased the count in 29 per cent of the rats and brought increased quantitative growth in 50 per cent. This was not statistically significant ($p > 0.05$). Amniotic membranes decreased the count in 58 per cent of the rats and only resulted in increased bacteria in 13 per cent of the rats. This proved to be statistically significant ($p < 0.01$).

By 96 hours, or following two changes of biological dressings, both human skin and amniotic membranes had decreased the bacterial counts in virtually all of the animals. Reduced counts were seen in only 40 per cent of the control group. Both of these differences were statistically significant ($p < 0.01$). Although the percentage of rats with decreased counts at 96 hours were almost equal with human skin and amniotic membrane, the degree of decrease was significantly greater with amniotic membranes. The geometric mean of the bacterial counts after two changes of human skin was 10^6 organisms per gram of tissue compared to 10^3 organisms per gram for the amniotic membrane treated group (Fig. 3).

Part "B"

The *in vitro* studies showed no antibacterial effect of either skin or amniotic membrane on the growth of *Pseudomonas aeruginosa* or *Escherichia coli*. Within 24 hours all cultures contained 10^8 organisms per milliliter. This was true irregardless of the initial inoculum or the type of tissue homogenate present (Table 2).

Part "C"

In the burned patients, the bacterial population was well controlled with the topical antibacterials. Bacterial counts were 10^5 or fewer organisms per gram of tissue

TABLE 2. *Effect of Biological Dressing Homogenates on Bacterial Growth in vitro.*

	Number of Bacteria After 24 Hours Incubation 37°C								
	Human Skin Homogenate					Amniotic Membrane Homogenate			
	Control	50 mg.	100 mg.	200 mg.	400 mg.	50 mg.	100 mg.	200 mg.	400 mg.
10^3	10^8	10^8	10^8	10^8	10^8	10^8	10^8	10^8	10^8
10^4	10^8	10^8	10^8	10^8	10^8	10^8	10^8	10^8	10^8
10^5	10^8	10^8	10^8	10^8	10^8	10^8	10^8	10^8	10^8
10^6	10^8	10^8	10^8	10^8	10^8	10	10^8	10^8	10^8
10^7	10^8	10^8	10^8	10^8	10^8	10^8	10^8	10^8	10^8
10^8	10^8	10^8	10^8	10^8	10^8	10^8	10^8	10^8	10^8
Initial Inoculum of Bacteria									

at the time the treatment was begun with the biological dressings. Both amniotic membranes and split-thickness homograft skin resulted in further decrease of the bacterial counts. In no instance did the bacterial count increase while biological dressings were being used. They appeared to be as effective as homografts in preparing the beds for grafting and in serving as a dressing to bide time while awaiting new donor areas for autografts.

Discussion

The concept of temporary biological dressings, introduced in the 1930's, has been developed to the point where their use has been extended from burns to all types of granulating wounds.[26] Homograft and heterograft split-thickness skin have both proved to serve the functions required of a biological dressing. However, each has its drawback. Originally, homografts required that another individual donate his skin as a life-saving measure. This often meant up to 20 to 30 donors to deal with for a single patient with major burns. In 1953, Brown *et al.*[4] reported that it was practical to use postmortem homografts as biological dressings. Since that time, cadavers have provided the usual source for homografts. In the general hospital, however, the supply of cadavers suitable to provide sufficient homografts is limited. Those cadavers with a history of malignancy, hepatitis, or syphilis are usually excluded. Personnel must be kept available at all times to procure the skin in a sterile manner, often in the operating room.

Following the recommendations of Silvetti *et al.*[28] heterografts were introduced to eliminate the problem of a lack of available homografts. Porcine heterografts are now commercially available. They are not, however, always immediately available when needed, and when purchased, add to the already overwhelming cost incurred by the burned patient. Additionally, heterografts have not proved as effective as homografts in decreasing bacterial contamination of the wounds in our hands.[23] Both homografts and heterografts are limited by the size in which they are available. The size and shape being determined by the existing dermatomes being used to obtain them.

Amniotic membranes were chosen for evaluation in the present study because of their ready availability, large size, lack of cost, and their structural similarity to skin. Histologically the membranes are made up of two loosely connected tissues, the amnion and the chorion. The amnion or inner layer is derived from the epiblast and is continuous with the ectoderm or the embryo.[1,25] Its inner surface is composed of cuboidal or flattened epithelial cells and its outer surface covered with mesenchymal connective tissue. The chorion has mesenchymal connective tissue in contact with the amnion and an external ectoderm composed of a fairly thick layer of transitional epithelium. Pigeon[20] has stated that since amniotic membrane is formed by the ectoderm of the fetus, it is like an extension of the baby's skin.

Amnion, chorion, and the combined amniotic membranes have been used by various investigators as a substitute for skin in the past. Most investigators have had a preference for one or the other of the membranes. Jenner[16] studied amnion and chorion side by side in the same wound and found no demonstrable difference between the two. Similarly, Dino *et al.* experimented with various layers of fetal membranes and found the end result practically the same whether using amnion alone, chorion alone, or combined amnion and chorion.[9] Since Sabella's first case describing the use of amniotic membrane on the burn wound 50 years ago, multiple reports have appeared in the world's literature. Most of these were reporting the attempts to use amniotic membrane as a permanent substitute for skin autografts or as a dressing over partial-thickness burns. Pigeon[20] has demonstrated their value in partial-thickness burns as a cover under which reepithelialization can occur. Their use in full-thickness skin loss has not been rewarding. Dahinterova and Dobrkovsky[6] observed failure when amniotic membranes were applied on deep burns or on seriously infected areas. They found that the membranes became autolyzed in 48 hours and disintegrated. Furthermore, they stated that the same was true on all granulating surfaces even if they were clean. Similar findings have been reported by others.[9,20,29] In all of these studies, the amniotic membranes were left in place until disintegration occurred. Once the softening and dissolution process begins, it seems obvious that any beneficial effect of the amniotic membrane would be negated. Therefore, in the present study, the membranes were changed every 48 hours. As demonstrated by Shuck and Moncrief[27] for homograft skin, in a less tidy wound more frequent changes prevent collections of purulent material from developing under the biological dressing. This allows for firm adherence of the membrane to the underlying granulations. In the present studies, no disintegration occurred within 48 hours when adherence of the membrane was maintained.

Because of the occasional positive cultures discovered in the amniotic membranes prepared for laboratory use in sterile saline, those prepared for clinical use underwent a slightly different preparation. Dino *et al.* have reported the testing of many agents to sterilize amniotic membranes. They found sodium hypochlorite effective. It is felt that a single rinse of 0.025 per cent sodium hypochlorite together with rinses of sterile saline, will not change the biologic effectiveness of the amniotic membrane to any significant degree.

Frequently changed amniotic membranes were more successful in decreasing the bacterial count in contaminated rat burns than was human skin (Fig. 3, Table 1). This raised the question as to whether there was a substance in amniotic membrane which was specifically antibacterial. One such possibility is allantoin, which is known to exist in amniotic membrane. Needham[19] reported studies by A. W. A. Brown showing the beneficial effect of maggots on contaminated wounds was due in part to the allantoin and urea excreted by them. Another possibility is lysozyme, a bacteriolytic protein of low molecular weight which is present in amniotic tissues.[13] To test for the presence of such a subcellular substance being responsible for the increased antibacterial effect seen in rats, amniotic membrane homogenate was compared to human skin homogenate *in vitro*. The complete lack of any demonstrable effect on bacterial growth by the varying dosages of tissue homogenate was not unexpected (Table 2). Rubin and Bongiovi[24] recently stated that skin itself possesses bactericidal substances in its biological makeup such as lysozymes and certain fatty acids. Neither, however, could they demonstrate bacterial inhibitory activity of split-thickness human skin *in vitro* when measured by a disc sensitivity technic.

Another hypothesis for the observed decrease in the bacterial count under the amniotic membrane lies in the intimate biologic closure of the open wound by the membrane.[18] Restoration of the functional circulation through the covered granulations allows a more rapid turn-over of phagocytes, serum bacteriolytic factors, and may accelerate the removal of the necrotic debris. Therefore, repeated applications of the membranes allow the host resistance factors in the granulating bed to function at peak efficiency. This same mechanism of obtaining a biologically closed wound would function, not only for amniotic membranes, but also for other temporary biological dressings. The same hypothesis could thus be used to explain the effect on the bacterial count seen in rats treated with human skin. The increased antibacterial effect seen with the amniotic membrane may be due to the fact that it is less well-differentiated than skin. Although the amniotic membranes used on the rat were from human sources and therefore heterologous as was the skin; Douglas *et al.*[11] have shown that there is very little difference between the heterologous and homologous chorion grafts in the mouse. This is compared to a threefold difference that they demonstrated between heterologous and homologous skin. In the present experiment, the amniotic membrane may have had an effect in the rat comparable to rat homograft skin and therefore greater than human heterograft skin. Rappaport *et al.*[21] have shown that heterograft left in place longer than 24 hours, as we might normally use a homograft, often will not control the underlying infection. This correlated with data of our own showing that homografts are more effective than heterografts in decreasing bacterial growth in both laboratory animals and in the clinical situation.[23]

The nonuniformity of a clinical burn make comparative studies in the clinical situation difficult to interpret. Although the number of patients and comparative observations were too small for statistical analysis, amniotic membranes appeared to decrease the bacterial count in the burn wound at least as well as homografts. In patients, significant gross infection is not often present in the burn wound managed with topical antibacterials. Therefore, any changes due to biological dressing will be of small magnitude and will require a great many observations to obtain statistically significant data.

The amniotic membranes fulfilled all of the functions of an ideal biological dressing. In terms of their large size and ready availability at no cost to the patient, they are actually superior to homograft and heterograft skin. In addition, the membranes appear to have another property. Subjectively the rapidity of ingrowth of epithelium form the borders of the wound in full-thickness defects and the rate of re-epithelialization of partial-thickness burns appear to be increased by their use. Chao *et al.*[5] and Troensagaard-Hansen[31] also have noted that amniotic membrane seemed to possess some specific healing power. They have reported a stimulation of both fibrous-tissue growth and more rapid epithelial repair. Needham[19] has summarized the available information on the growth-promoting factor found in embryo extract. Although the available evidence seems to point to an acceleratory action of amniotic membranes on the healing of wounds, that phase of their action was not objectively studied in the present investigation.

Summary

Amniotic membranes have not previously been studied using the standard methods currently in vogue for biological dressings. The present study has evaluated amniotic membranes changed every 48 hours on a standard infected escharectomized scald burn in the rat. Compared to human skin the amniotic membrane was more effective at decreasing the bacterial counts in the burn wound. A specific antibacterial substance was sought using *in vitro* technics with amniotic membrane homogenate. No such substance was found. It is proposed that the *in vivo* antibacterial effect seen is due to the achievement of a biologically closed wound by the membrane, thus allowing the host's own defense mechanisms to deal with the bacterial population as did other biological dressings. However, their large size, ready availability, and lack of cost make them more desirable.

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Focal Nodular Hyperplasia of the Liver

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THE ETIOLOGY of focal nodular hyperplasia of the liver remains undetermined. Its various synonyms: adenoma, hamartoma, benign hepatoma, solitary hyperplastic nodule, focal cirrhosis, cholangiohepatoma, and mixed adenoma, attest to this fact. Edmondson,[6,7] who has been the major contributor to the understanding of this lesion, believes it to be a response to focal parenchymal injury. The hypothesis that the lesion may result from arterialization by an anomalous arterial supply of a localized region of liver tissue will be developed in this paper using four cases in which two had the lesion demonstrated by arteriography. In addition, since the prognosis in individuals with this lesion has been questioned, two of the cases with 5- and 6½-year follow-up observations will be used to substantiate its benign nature.

It appears very clear that individuals may harbor this lesion without complications for many years since it has been noted as an incidental finding at autopsy. In such a series 34 lesions of focal nodular hyperplasia were reported.[3] In all cases the lesions at autopsy were incidental findings and had not produced symptoms. The lesion occurred in 15 men and 19 women who died between the ages of 27 and 74 years. Conversely, such lesions may become symptomatic: by virtue of size, as an abdominal mass; by torsion if the lesion is pedunculated, producing infarction and pain; or by rupture through the capsule, resulting in intraperitoneal hemorrhage. The lesions, if they are to become symptomatic, do so usually in childhood; clinical cases, therefore, range in one series of eight patients from 7 months to 14 years.[6] In our four cases, one adult patient was asymptomatic, the lesion being noted on arteriographic studies performed for another reason; the second adult case and the two cases in children were symptomatic with palpable upper abdominal masses.

Case Reports

Case 1. A 36-year-old woman, mother of six children, had a retrograde aortogram during a work-up for recurring pyelonephritis and calculi in the upper pelvis of a double left renal pelvis. Although no significant abnormal renal vasculature was demonstrated, two incidental aortographic findings were noted: (1) A well-vascularized hepatic tumor in the lateral aspect of the right lobe and (2) a non-calcified splenic artery aneurysm. Liver function tests were normal and peripheral blood counts were normal Roentgenographic studies of the chest and of the gastrointestinal tract were normal. Physical examination, except for a mild elevation of blood pressure of 146/94, was normal. Neither liver, spleen, nor abnormal abdominal mass were palpable.

In the aortogram, the right hepatic artery was noted to branch into three large tortuous branches a short distance within the liver hilus (Figs. 1A and 1B). These branches did not branch or taper normally (Figs. 1B and 1C). After initial divergence one from the other, the branches converged laterally to produce a vascular "blush" in a moderately large tumor at the lateral periphery of the right hepatic lobe (Fig. 1D). Evidence of arteriovenous communications in the tumor was not seen nor was there early venous filling.

Preoperative evaluation of the aortogram did not help to distinguish a benign from a malignant tumor since either lesion could present as a well-vascularized lesion by aortography.

The operation, under hypothermic conditions and general

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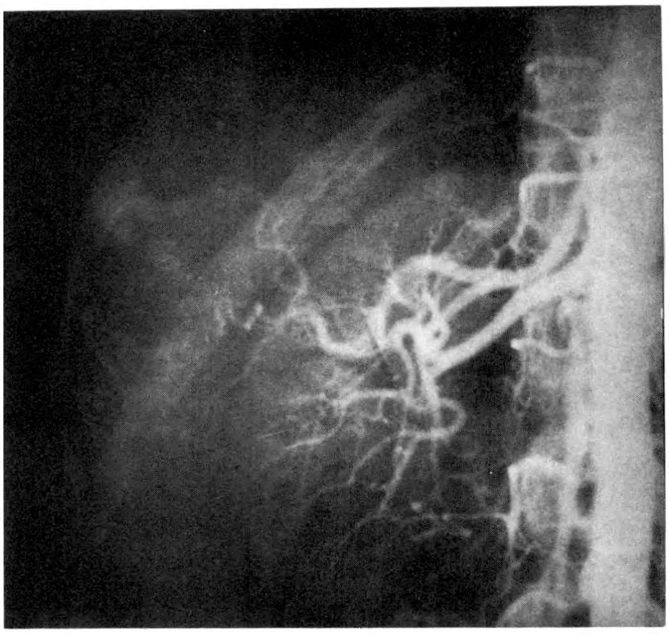

FIG. 1A. Case 1. Aortogram demonstrates the right hepatic artery trifurcating into anomalous arteries.

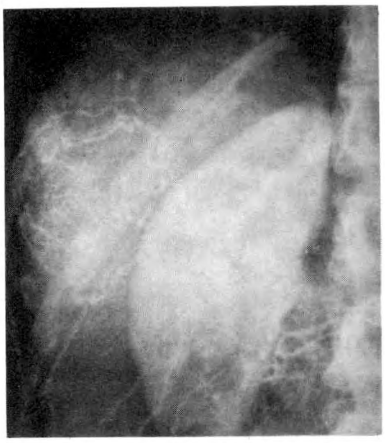

FIG. 1C. The anomalous branch arteries have converged at the periphery and a faint plexiform network of small vessels is seen.

anesthesia, was performed through a right thoracoabdominal incision, dividing the diaphragm. A tan, raised, slightly firm tumor was found in the anterior segment of the right lobe of the liver (Fig. 2). This segment, containing the tumor, was resected. Several moderately large arteries supplying the lesion were ligated in performing the resection. Following hemostasis to the raw liver surface, the 2 cm. splenic artery aneurysm was resected after ligating the artery proximally and distally. Splenectomy was not considered necessary since collateral circulation to the spleen through the vasa brevia was thought to be adequate.

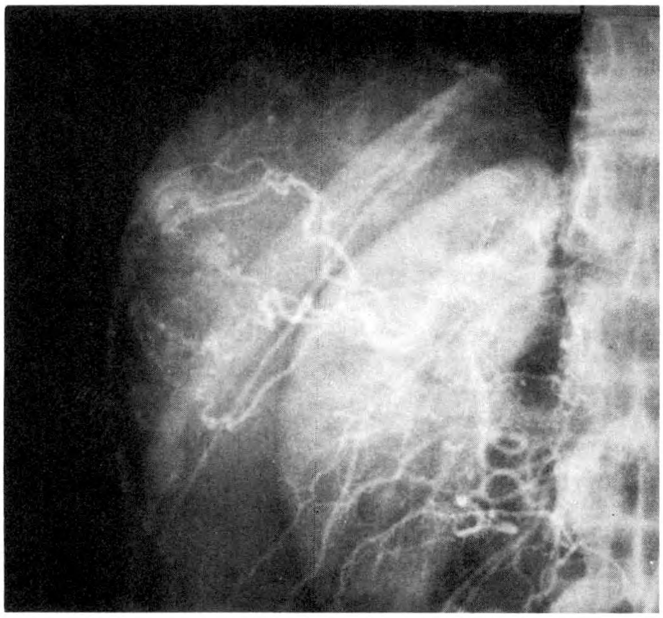

FIG. 1B. A later film shows the anomalous arteries to be tortuous and to extend to the periphery of the right lobe without normal tapering.

The postoperative course was complicated by thrombophlebitis of the deep veins of the right leg, noted on the fifth postoperative day. Pulmonary embolism ensued and dextran was employed. The clinical course remained stable until the eleventh postoperative day when sudden left upper quadrant and lower left chest pain supervened. Splenic infarction from devascularization of the spleen secondary to splenic artery ligation and inadequate collateral circulation was suspected. However, a left lower lobe pulmonary infarction secondary to a second pulmonary embolus could not be ruled out. The former explanation was proven at laporatomy performed that same day and a splenectomy was performed. Plication of the inferior vena cava with a Miles clip was performed to protect against further pulmonary emboli. Heparin administration was not favored because of the recent major liver resection and the even more recent splenectomy. The remainder of the hospital course was uneventful and the patient was discharged on the 22nd postoperative day. She has been well for the past 2½ years.

Pathologic Findings. The specimen was a segment of the right lobe of the liver, measuring 12 × 8 × 6 cm. Near one edge beneath Glisson's capsule was a 4 × 5 cm. lobulated, firm, pale tan mass. The vessels over the surface were prominent. The tumor extended 3 cm. into the parenchyma. The border was distinct and pseudoencapsulated. The surrounding hepatic parenchyma was brown and had a discernible lobular architecture. Several dilated vascular channels were apparent grossly in the adjacent liver but were not present in the tumor (Fig. 3A). The tumor was composed of small, irregular nodules which were separated

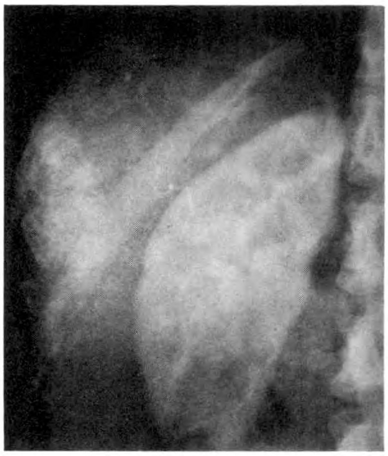

FIG. 1D. In a late film the vascular "blush" of the peripheral tumor is seen. There is no early venous filling.

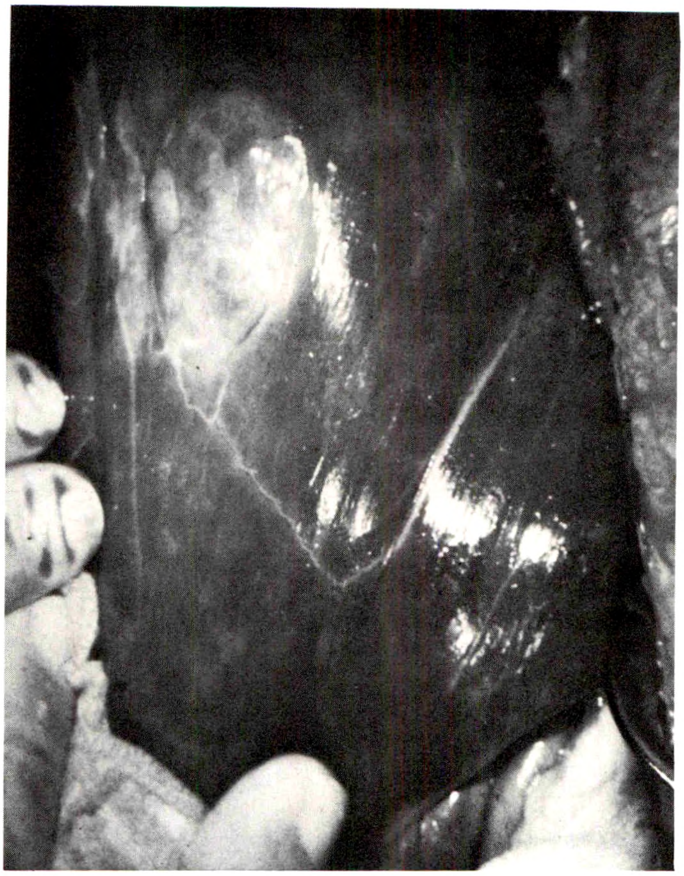

FIG. 2. Case 1. The pale tan, bulging, nodular mass in the anterior segment of the right lobe of the liver, demonstrated during the operation, is typical of focal nodular hyperplasia but cannot be definitively distinguished from a malignant tumor by gross characterization. The lesion is only slightly less compressible than the surrounding normal liver tisue.

by thin bands of fibrous tissue. The tumor was firmer and paler than the surrounding parenchyma. Upon histologic study a pattern of micronodular cirrhosis was present with numerous hyperplastic regenerative nodules surrounded by bands of fibous tissue, generally thin and narrow, but occasionally rather broad (Fig. 3B). The hepatocytes were swollen, with clear cytoplasm, resembling glycogen, and were arranged in slightly disorganized plates. Central veins were not present in the nodules (Fig. 4A). Occasional clusters of proliferating bile ducts were present at the periphery of nodules but no bile stasis was noted. Focal aggregates of lymphocytes infiltrated the fibrous tissue septa. The most significant change in the tumor was a marked mural thickening of blood vessels within the tumor, especially prevalent at the interface between tumor and normal liver. The thickening appeared due to fibromuscular proliferation in the media, generally pushing the intima inward and sparing the outer media. The proliferation was both concentric and eccentric, sometimes producing slit-like lumina. Occasionally, complete occlusion was noted (Fig. 4B). There was no necrosis or inflammation of the vessel walls. Whether or not these vessels were arteries or veins could not always be determined; elastic stains generally showed no clearly definable elastic tissue in the thickened walls. Some involved vessels were clearly arteries which showed some local intimal thickening also. There was no evidence of thrombi in the vessels. A dilated channel seen grossly appeared to be a lymphatic. In the grossly normal liver tissue the vessels showed no specific changes and the hepatic tissue histologically also was unremarkable. Focal nodular hyperplasia of the liver was the final diagnosis.

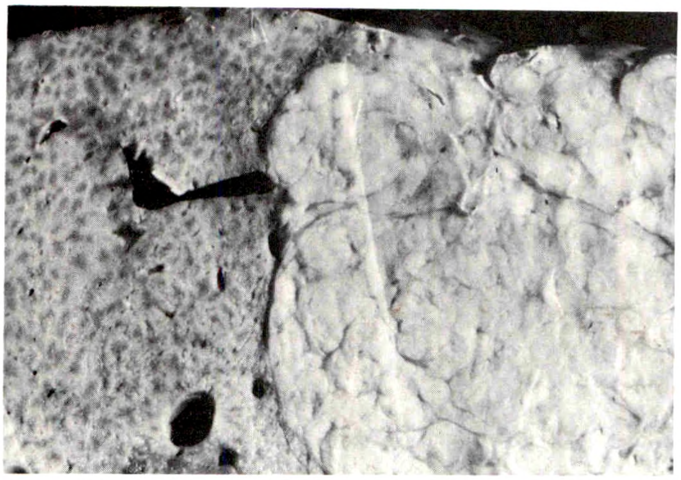

FIG. 3A Case 1. The gross specimen at the junction between normal liver, left, and the lesion of focal nodular hyperplasia demonstrates the discrete margin of the lesion and evidence of passive congestion in the normal liver but not in the lesion. Dilated vascular channels or lymphatics are noted at the periphery.

Comment. The asymptomatic lesion of focal nodular hyperplasia in this case was correlated with arteriographic findings of an arterial anomaly. This anomaly produced an arterialized locus within the right hepatic lobe. Histologic evidence of an increase in the number

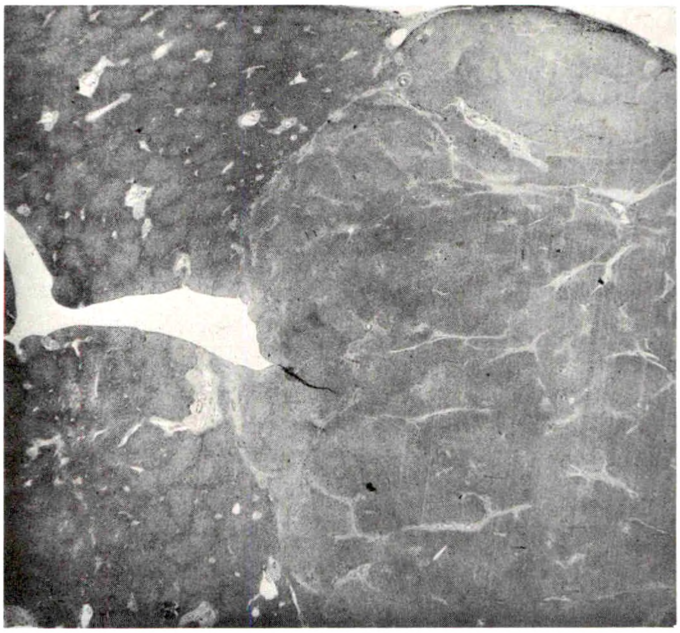

FIG. 3B. A low-power photomicrograph demonstrates that the lesion consists of multiple disorganized regenerative nodules separated by fine fibrous septa. The lesion does not possess a true capsule. Numerous dilated vessels are noted within the lesion and within normal liver tissue at its periphery (H&E ×6).

of dilated blood vessels and of marked medial fibromuscular proliferation of blood vessels suggested chronic arterialization. Regenerative nodules of hepatocytes and increased fibrous tissue proliferation further suggested the effects upon hepatic parenchyma and stroma of this chronic increase in arterial pressure. Secondary ischemic changes may result from the progressive narrowing of arterial and venous lumina.

Case 2. A 21-year-old housewife was referred to Walter Reed General Hospital with hepatomegaly of uncertain etiology. This finding was first noted 7 months prior to this admission during the second month of pregnancy. At that time laparotomy was performed and a tumor involving the entire left lobe of the liver was noted. The right lobe was normal but displaced posteriorly and superiorly by the enlarged left lobe. Biopsy of the left lobe suggested a diagnosis of focal nodular hyperplasia. Pregnancy was allowed to proceed to term and a normal vaginal delivery eventuated 2 months prior to admission. Hepatomegaly increased and the liver mass became tender. There was no history of hepatitis, excessive alcoholic intake or intake of hepatic toxins.

Physical examination confirmed the enlarged liver which extended to a point four fingerbreadths above the right iliac crest and, in the epigastrium, to a point three fingerbreadths below the xiphoid process. The liver surface was firm, irregular, and slightly tender; and a loud systolic bruit was present in the epigastrium with radiation to the right upper quadrant and flank. A healed right subcostal incision, the result of recent laparotomy, was present. No abnormal thoracoabdominal venous pattern was seen. The spleen was not enlarged and lymphadenopathy was absent. The remainder of the examination was within normal limits.

Laboratory studies of liver function were normal except for liver scintiscan. The liver scan was deceptive, demonstrating poor uptake in the tumor mass believed to be present in both lobes. Normal uptake was present only in a localized area just beneath the right diaphragm. In retrospect this normal uptake was present in the markedly displaced normal right lobe. Hepatic angiograms showed markedly enlarged common and left hepatic arteries with displacement, to the right, of the entire left lobe, particularly the medial segment. The right hepatic artery is of normal calibre (Fig. 5A). A diffuse, but roughly lobular "blush" was seen in the well-vascularized left lobar hepatic lesion in the late sequences of the angiograms (Fig. 5B).

Review of the liver biopsy specimen confirmed the diagnosis of focal nodular hyperplasia. The marked arterial changes in both the biopsy specimen and the angiographic studies suggested a massive hemangiomatous lesion requiring surgical resection. The increasing size of the lesion and increasing abdominal discomfort prompted surgical exploration and resection.

After a 2-week diagnostic evaluation, exploration of the liver through a right thoracoabdominal incision was performed. The lesion was found to be confined to the left hepatic lobe, the normal right hepatic lobe being displaced posterolaterally to the right. Left hepatic lobectomy was attempted using total hepatic inflow occlusion. Excessive bleeding from the hepatic venous system was encountered, necessitating 22 units of blood. Hemostatic control was unsuccessful and cardiac arrest supervened. Resuscitation was unsuccessful. The patient died on the operating table.

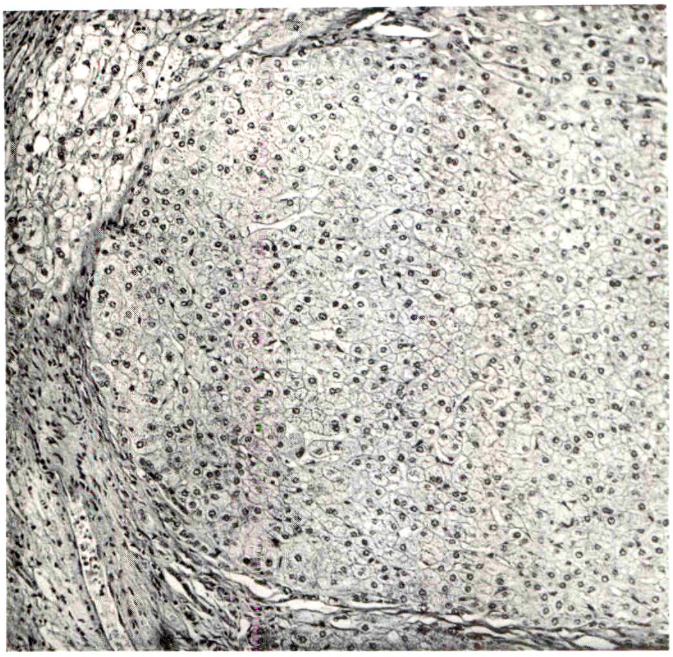

FIG. 4A Case 1. High-power photomicrograph of one of the regenerative nodules shows an absence of the normal lobular architecture. The hepatocytes are large with clear cytoplasm, resembling glycogen. Central veins are absent (Masson Trichrome ×160).

Post-mortem examination confirmed a normal remaining right lobe of the liver. The resected left lobe of the liver showed an irregular knobby surface with nodules of varying sizes separated by strands of fibrous tissue. Prominent vessels were noted within the lesion and on the surface of the liver. The entire left lobe was replaced by the lesion. The right lobe was normal. Histologic studies demonstrated, in addition to characteristic findings of focal nodular hyperplasia described in Case 1, fatty infiltration of hepatocytes in some areas and glycogen-laden hepatocytes in others.

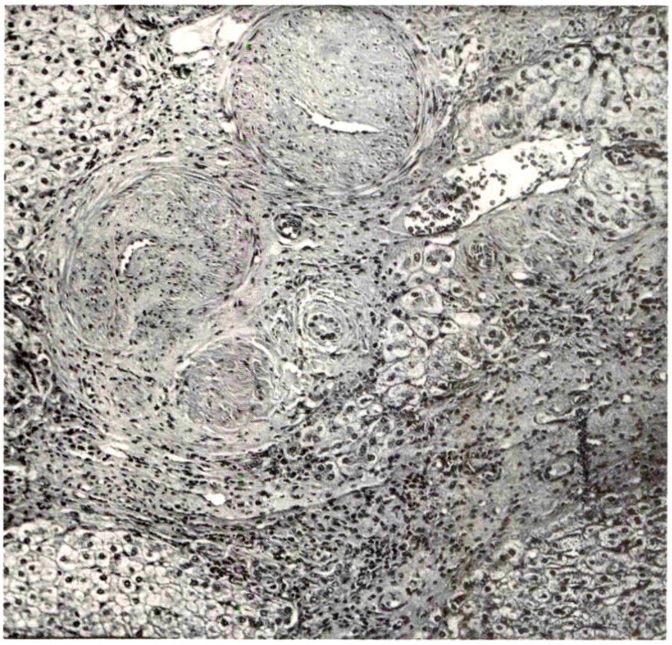

FIG. 4B. High-power photomicrograph demonstrates dense fibrous septa with chronic inflammatory cell infiltration and, most significantly, fibromuscular proliferation of vessel walls involving the media and subintima. Lumina are reduced to eccentric slits or are completely obliterated. (H&E ×160).

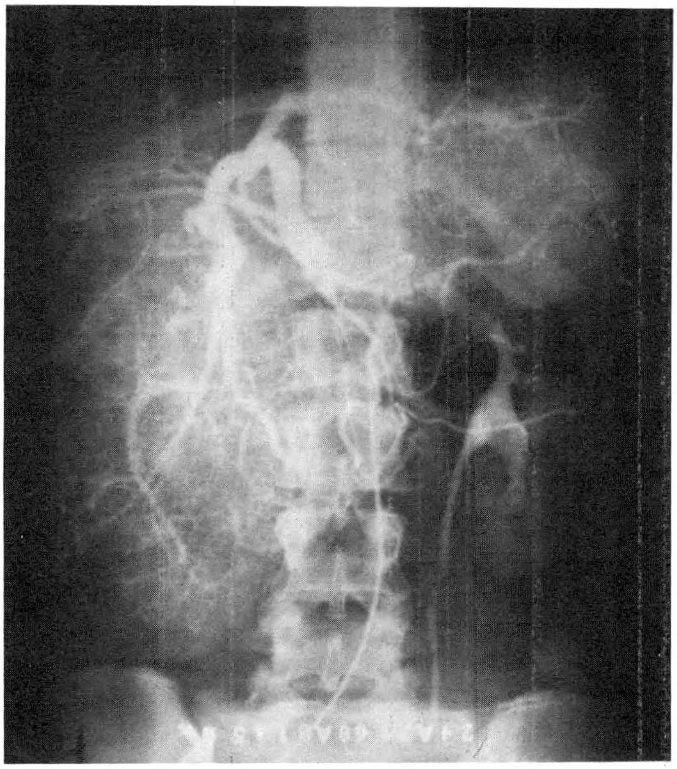

FIG. 5A Case 2. Hepatic angiogram demonstrates hugely dilated common and left hepatic arteries and a normal right hepatic artery and vasculature, albeit compressed by the greatly enlarged left lobe. The segmental arteries of the left lobe, the lateral segment artery and the medical segment artery, displaced to the right, are supplying the enlarged left lobe. Increased vascularity and anomalous branching and arching arteries supplying the lesion of focal nodular hyperplasia are clearly seen.

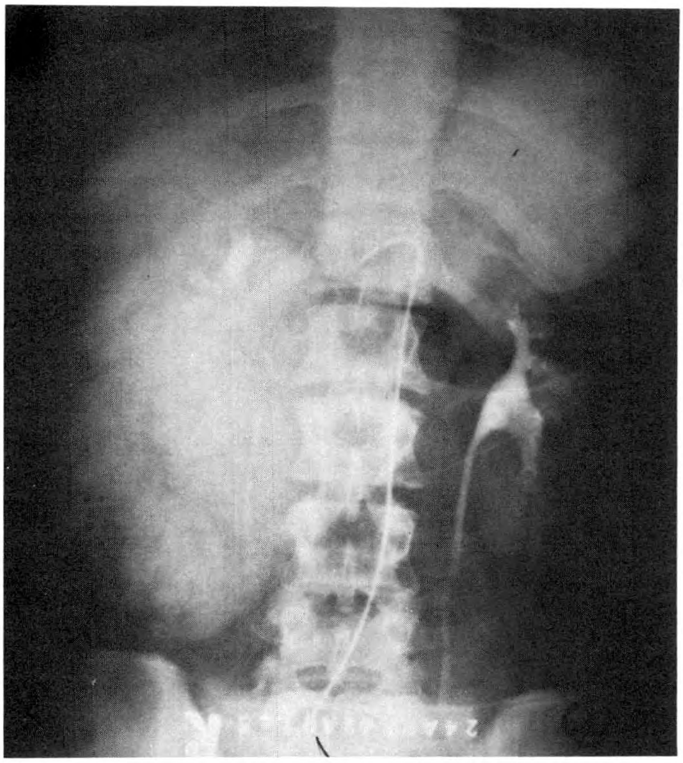

FIG. 5B. A later sequence demonstrates well-vascularized lobular architecture of the left hepatic lobe.

Comment. This case demonstrates conclusively the contribution and probable pathogenetic significance of the anomalous arterial blood supply to the left lobar lesion of focal nodular hyperplasia. The dilated left hepatic arterial vasculature suggests increased arterial flow. The possibility of arterial dilatation proximal to arteriovenous communications must be borne in mind but is not proven. Early venous filling was not demonstrated.

Case 3. A 7-year-old girl was referred to Walter Reed General Hospital on 3 August 1962 because of a mass in the midepigastrium noted 4 weeks previously. The mass had been discovered by a physician during a physical examination performed when the child developed measles. The mass was described as "lemon-sized," nodular and attached to the left lobe of the liver. Gastrointestinal x-rays were normal. Liver function tests were normal. A liver scan, using ^{198}Au, demonstrated a large area in the left lobe which failed to take up the radioactive material. There appeared to be encroachment also upon the right lobe.

Through a right thoracoabdominal incision a nodular, subcapsular tumor, measuring 10 cm. in greatest diameter, occupied almost the entire anatomic left lobe of the liver. It was light tan and pseudoencapsulated. Anatomic left lobectomy was performed. The child had an uncomplicated postoperative course and was discharged on the 13th postoperative day.

Pathologic Findings. A diagnosis of focal nodular hyperplasia of the liver was made (Figs. 6A and 6B). Dilated vessels were noted also in this case (Fig. 6C). However, no medial proliferation was seen. Hyperplastic nodules of regenerating liver cells were surrounded by fibrous strands containing lymphocytes and many proliferating bile ducts (Fig. 7A). No central veins were seen in the hyperplastic nodules, which consisted of solid masses of hepatocytes with large amounts of clear but granular cytoplasm. Prominent nerve fibers and dilated lymphatics were present in loose connective tissue adjacent to the "tumor" (Fig. 7B).

This patient has been studied several times since that time, the most recent occasion being 1 April 1969, almost 6 years and 7 months since resection of the tumor. Liver regeneration has proceeded normally as evidenced by scintiscan. There has been no evidence of recurrence of the tumor or development of other tumors in the remaining liver tissue.

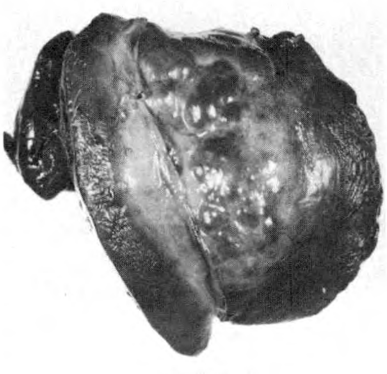

FIG. 6A. Case 3. The gross specimen consists of the anatomic left hepatic lobe and resembles a primary hepatoma. The liver capsule is raised by a lobulated, tan lesion with prominent surface vasculature.

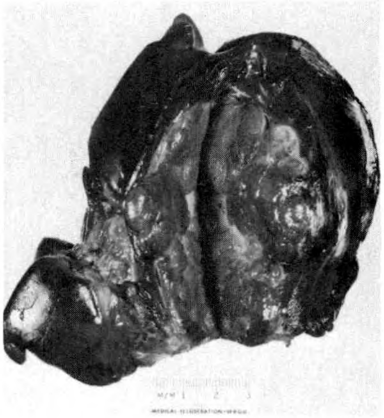

Fig. 6B. The gross specimen has been incised, demonstrating pseudo-encapsulation of a tan tumor mass which bulges on the surface. The consistency is only slightly firm. Central fibrosis extending outward into the lesion resembles the classical stellate fibrosis of focal nodular hyperplasia.

Comment. In this childhood case the presenting symptom was a palpable epigastric mass, the most common presenting complaint noted in other series. Resection of the left hepatic lobe within which the tumor occupied approximately 75 per cent of the volume, has resulted in an excellent outcome. Follow-up at 6½ years demonstrates no evidence of recurrence and normal growth and development of the child. Dilated vascular and lymphatic channels were also seen in this case although precise documentation by radiography of increased and anomalous arterial blood supply to this region of the liver is lacking.

Case 4. A 6-year-old girl was admitted on 30 January 1964 to Martin Army Hospital, Fort Benning, Georgia, because of a mass in the right upper quadrant of the abdomen. She had been examined a few days previously because of fatigue and a poor appetite of 2 months' duration. The mass was attached to the right lobe of the liver and was 6 cm. in diameter. The remainder of the physical examination was normal. Laboratory work-up was within normal limits with normal liver function tests and peripheral blood counts. Liver scan or hepatic angiogram were not performed.

At operation on 3 February 1964 a 6 cm. in diameter tumor

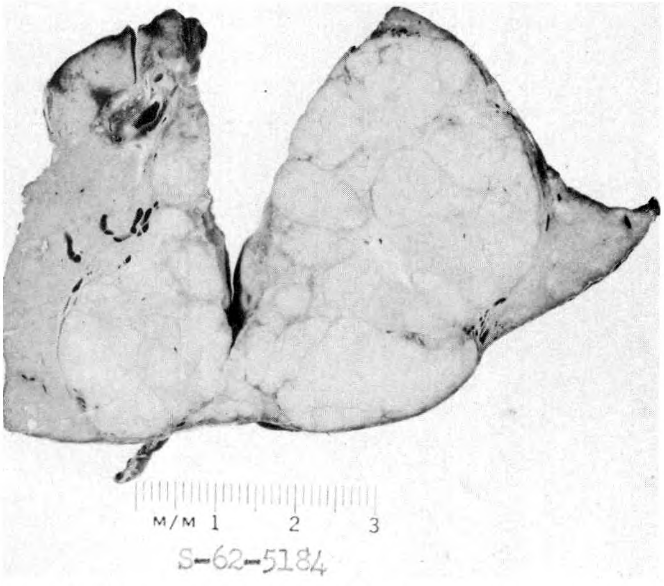

Fig. 6C. The cut surface of the fixed gross specimen accentuates the increased vascularity noted around the periphery of the lesion. The multiple irregular regenerative nodules of the larger mass lesion is shown.

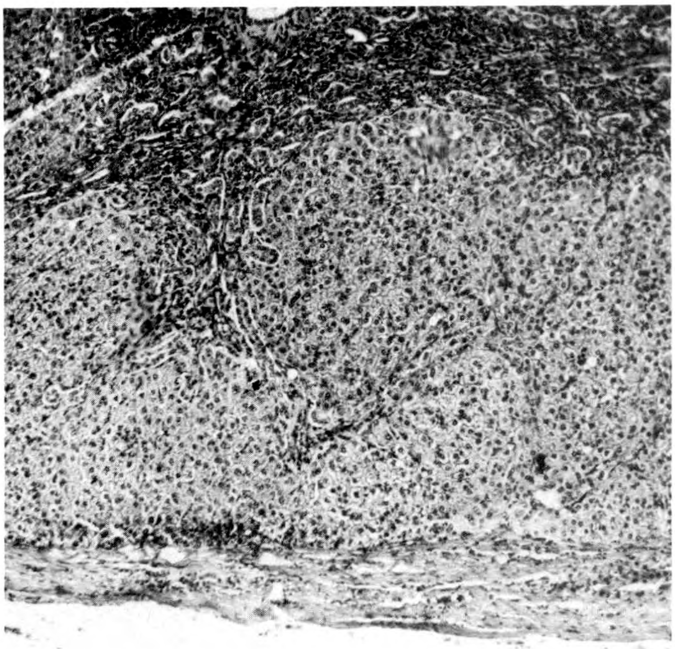

Fig. 7A. Case 3. Photomicrograph demonstrates regenerative nodules surrounded by fibrous tissue septa, heavily infiltrated with lymphocytes and containing many proliferating bile ducts. There is no normal lobular architecture and no central hepatic veins (H&E ×50).

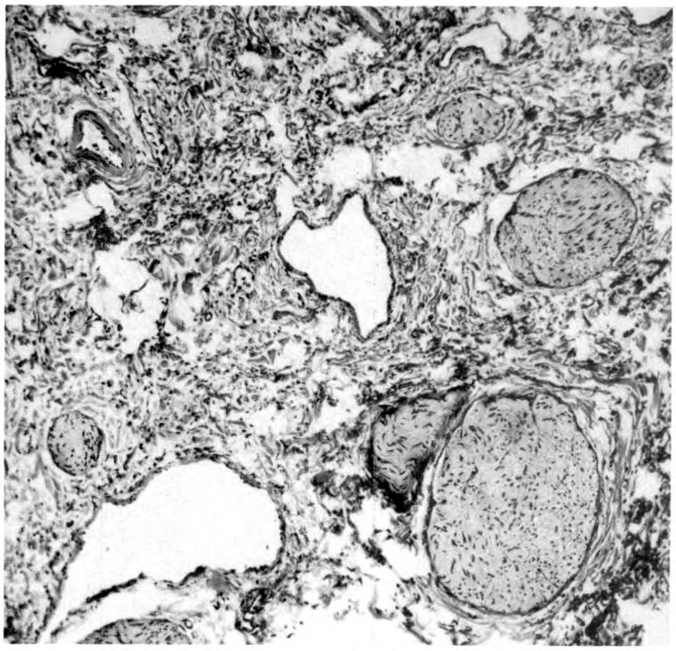

Fig. 7B. In an area adjacent to the "tumor" loose connective tissue contains dilated lymphatics and nerve fibers. The significance of these latter structures is not known (H&E ×20).

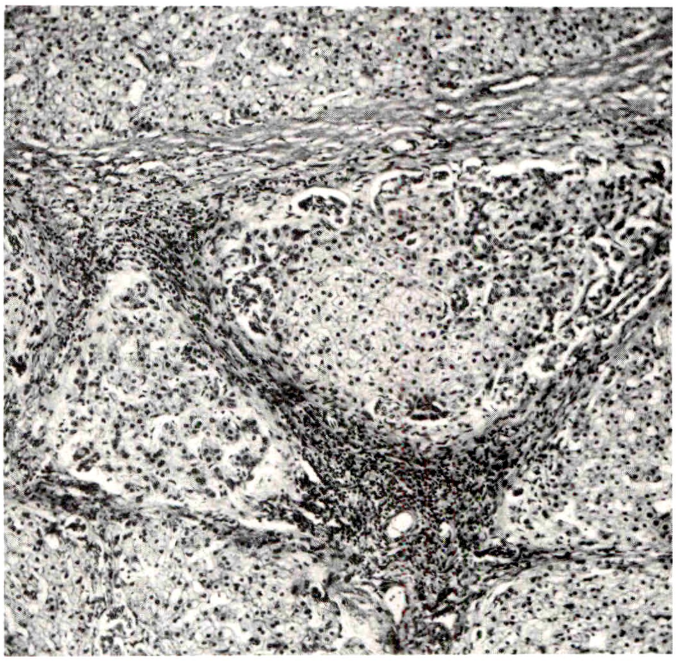

FIG. 8A Case 4. Photomicrograph demonstrates multiple nodules separated by broad bands of fibrous tissue containing lymphocytes. Many proliferating bile ducts are seen at the periphery of the nodules. The nodules noted in this field are smaller than many others in this case (H&E ×50).

mass arose from the medial and inferior portion of the right hepatic lobe. Right hepatic lobectomy was performed as the lesion was thought to be malignant. A low-grade subphrenic infection, necessitating prolonged drainage and antibiotics, complicated the postoperative course and delayed discharge from the hospital until the 21st postoperative day.

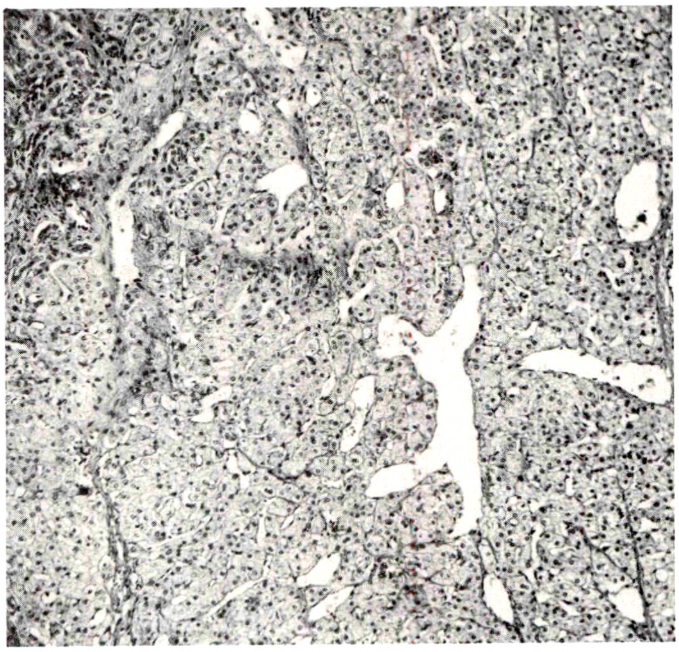

FIG. 8B. In the liver immediately adjacent to the "tumor" dilated veins and sinusoids are seen (H&E ×50).

Pathologic Findings. The microscopic studies of the specimen showed multiple coalescent nodules surrounded by broad bands of fibrous tissue, infiltrated with chronic inflammatory cells and containing many proliferating small bile ducts (Fig. 8A). Again dilated blood vessels, both thick-walled and thin-walled, were conspicuous within and just adjacent to the regenerative nodules. Dilated sinusoids were also seen (Fig. 8B).

This patient was operated upon in 1964 by Dr. Jay Fish, then stationed at Fort Benning, Georgia. She became known to the authors through our patient in Case 1 who, in 1969, was a next-door neighbor in Honolulu, Hawaii, of the patient in Case 4. On comparing notes of their "liver operations" it became apparent that both had had relatively rare lesions of focal nodular hyperplasia. The patient in Case 4 was then seen in follow-up in the spring of 1969 by the authors. It was then slightly over 5 years from operation, she had no evidence of recurrence and was in excellent health.

Comment. The presenting complaint was an abdominal mass, as in the previous case. Dilated blood vessels, both thick-walled and thin-walled, were very conspicuous both within the regenerative nodules and adjacent to the nodules. In addition, dilated sinusoids were also seen. Similar findings have been demonstrated in animal experiments involving arterialization of the liver.[11,16,18,22]

Discussion

As data have accumulated there seems little evidence at variance with the benign nature of focal nodular hyperplasia of the liver. Two of our patients with 5- and 6½-year follow-ups, plus other published case reports[2,6,10] would support such an assumption. The autopsy series of Benz and Bagenstoss[3] in which such lesions were noted as incidental findings at post-mortem examination also suggest their benign nature. In some cases in which the lesion could not be surgically removed, patients have remained in good health.[7,12]

The etiology of these lesions, however, has been an enigma. A pure liver cell adenoma is a neoplastic process and should be distinguished from these lesions.[4,6] Begg and Berry[2] suggested the lesions to be the result of a focal injury with partial healing and regenerative pseudolobule formation. Benz and Bagenstoss[3] suggest that "a localized area in the liver may show a special predilection to injury on the basis of congenital abnormalities in the blood supply or biliary circulation to that region."

Evidence is accruing to suggest that an anomalous arterial supply to a focal area of the liver can and does produce the lesion of focal nodular hyperplasia. In addition to our patients in Cases 1 and 2, Palubinskas' case[15] and Aronsen's case,[1] all with arteriographic demonstration of the hepatic lesion, show increased anomalous arterial supply to the lesion. In Aronsen's case, a large shunt measured at 2.6 liters per minute was corrected to 1.2 liters per minute after resection of the lesion of focal nodular hyperplasia. In Palubinskas' case three separate lesions with three separate anomalous arteries were demnstrated. In many of the published cases, including also ur Cases 2, 3 and 4, dilated blood vessels have been nentioned in gross descriptions,[9,10,15,20] as well as in nicroscopic studies. Intraperitoneal hemorrhage has ocurred from erosion of prominent vessels on the surface f the lesions.[2] An association of focal nodular hyperplasia vith cavernous hemangiomas in the same livers has ocurred in 20.6 per cent of cases.[3] This percentage is coniderably higher than the occurrence of hemangiomas of he liver in routine autopsies.

In addition to the above direct evidence of the assocition of an anomalous and increased arterial supply with he development of focal nodular hyperplasia of the liver, here is indirect evidence from animal experiments to inlicate that arterialization of all or a portion of the liver roduces many of the changes noted in focal nodular yperplasia. The vascular changes which have been reorted in experimental studies are thickening of the walls f large and medium-sized portal vein branches,[11,16,22] ibrinoid necrosis of the walls of small arteries and eins[11,16] and occlusion of some of these branches, folowing encroachment upon the lumen by medial prolifration.[22] Dilation of sinusoids has been described.[18] Secndary changes upon the hepatic parenchyma have not een predictable although in dogs examined 5 years after erformance of hepatic artery-portal vein anastomosis atty infiltration and fibrosis have been demonstrated.[18] n animals having one lobe arterialized, decrease in lucose-6-phosphatase activity suggested injury and hange in the endoplasmic reticulum.[22] Chronic inflamnatory infiltrate, fibrosis, and proliferating bile ducts ave been demonstrated in some of the animals studied everal months to years following arterialization.[18,19,22] ross cirrhosis was produced in one animal.[19]

In a clinical case of congenital telangiectasia, involving he liver, profound hepatic changes were produced by hronically elevated pressures in the hepatic vasculaure.[21] Fibrosis, both portal and intralobular, was marked. hese fibrous strands contained proliferating bile ducts nd separated nodules of regenerating liver lobules. Some iver plates were normal but others were atrophic in reas where sinusoidal dilatation and congestion were resent.

In a recent study occlusive arteriopathy of capsular essels was associated with adrenal cortical hyperplaia.[5] The author theorized that hyperplasia occurred to ompensate for areas of ischemic atrophy secondary to he obliterative vessel changes.

The exact mechanism for the parenchymal changes in he liver leading to focal nodular hyperplasia cannot be ositively identified. There are at least two possible echanisms. The lesion may be due to injury secondary o increased pressure in the sinusoids and portal vein ranches from chronic exposure to arterial pressure. Late occlusive lesions in the small arteries and veins may produce subsequent ischemia, followed by atrophy and compensatory regenerative nodules. The lesion, on the other hand, may be explained by the fact that the vascular anomaly is, in fact, a focal arteriovenous malformation. Shunting of blood away from a localized area of liver may produce subsequent ischemia with its previously-noted effects. Arteriographic findings demonstrate opacified blood in the lesion. This finding suggests either an increase in vascular supply or a stasis of blood flow. An arteriovenous shunt was calculated in Aronsen's case with correction after resection of the lesion. It is conceded that many tumors, including hepatoma, during their development, form arteriovenous communications. It is, therefore, possible that such connections developed as the lesion developed and were not the cause of the lesion. Since, however, the lesion bears a close resemblance to cirrhosis, albeit localized, and since studies of arterialization of the liver have produced similar injury, it is most tempting to incriminate a localized vascular anomaly which produces a focal injury and a focal hyperplastic lesion.

Vascular abberations associated with cases of focal nodular hyperplasia have been demonstrated by:

(1) Arteriography.

(2) The occurrence of the lesion in areas of hemangioma.[8,14]

(3) Frequent coexistence of hemangiomas and focal nodular hyperplasia in the same liver.[3]

(4) Findings at operation or in the laboratory of marked vascular changes in the arteries and veins supplying the lesion and within the lesion.[9,10,15,20]

(5) Calculation of a vascular shunt by BSP extraction and splanchnic blood flow technics.[1]

Summary

1. Four surgically treated instances of focal nodular hyperplasia of the liver are reported. Two of the lesions occurred in children and presented as upper abdominal masses. Both were believed to be malignant tumors and lobectomy was performed. Their benign nature was ascertained on histologic examination. A third lesion was noted as an incidental finding on aortography performed for another reason. In the majority of adult patients the lesion presents in this manner. In contrast, in a second adult patient (Case 2), the lesion presented as an upper abdominal mass. The lesion was localized to the anatomic left lobe. Arteriography demonstrated large dilated common and left hepatic arteries with a normal right hepatic artery. Inability to determine the exact nature of the tumor on arteriography has prompted abdominal exploration and resection.

2. An increased and anomalous arterial blood supply is a common denominator in cases of focal nodular hyper-

plasia. A theory of focal hepatic injury with ischemia, atrophy, fibrosis and regenerative hyperplasia, resulting from this anomalous blood supply, is developed.

3. The benign nature of the lesion is emphasized and substantiated from a review of the literature and from two cases with 5- and 6½-year follow-ups following resection.

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On the In Vivo Clearance and Detoxification of Endotoxin by Lung and Liver

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Braude and associates by using ^{51}Cr labeled endotoxin, a particulate lipopolysaccharide[20] derived from gram negative organisms, found that after its injection the label gradually disappears from the blood.[5,6] Beeson's studies were the first to indicate that this blood clearance occurs predominantly by phagocytosis.[1,2,3] The rate of disappearance is rapid if small sublethal doses of endotoxin are given. Following administration of larger quantities this process occurs at a much slower pace.[5,6]

The critical endotoxin dose, the absolute amount cleared from blood if all phagocytes come into play, is unknown. From previous observations we have to assume that it is relatively small. After an initial rapid phase, blood clearance for endotoxin proceeds more slowly suggesting that the actual pre-empting of the attachment sites on the phagocyte, incorporation by the cell and intracellular inactivation take place at relatively slow rates.

Rudback and Johnson[21] and Oroszlan[16] and associates demonstrated that the prolonged presence of endotoxin in blood is further enhanced through its association with and reversible inactivation by certain plasma proteins. Thus, under normal conditions, endotoxin in this form is hard to detect in plasma or serum. Special technics for its dissociation are required to release the lipopolysaccharide before it can react in certain identification reactions, *e.g.* the Limulus lysate test as recently described by Levin and associates.[15]

Braude *et al*,[6] found the liver to be the primary organ involved in the clearance of endotoxin. Previously, Waravdekar and associates,[30] Rutenburg *et al*,[22] Trapini and co-workers[28] as well as Corwin and Farrar[7] and Filkins[8] noted, however, that several organs or the homogenates prepared from these organs, including those *without phagocytic activity e.g.* the kidney, inactivate endotoxin *in vitro.* Hence the precise role of the liver in this process remains to be defined.

Recently we observed that gram-negative septicemia occurs in dogs during acute hepatic failure.[10] Subsequently Hume[13] and associates reported similar findings in man during hepatic failure. Bjorneboe *et al.*[4] and Triger and associates[29] noted in patients with hepatic cirrhosis that antibody titers for *E coli* were markedly increased. These various findings suggested that endotoxin may be responsible for some of the clinical manifestations of hepatic failure.

Potential sources of endotoxin are many, but because of their abundance the gram negative organisms of the intestine would seem to constitute a primary source. Previously Ravin *et al.*,[18] Sanford and Noyes[23] and Kocz-sar and associates[14] tried to demonstrate the absorption of endotoxin from the gut, nevertheless, there does not seem to be satisfactory unequivocal evidence for such a process at this time.

Assuming that intestinal absorption of endotoxin would take place under certain circumstances, the

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TABLE 1

Mode of Injection	Dose of Endotoxin	No. of Animals Studied	Mortality
Rapid Injection			
Endotoxin	1 μg/100 Gm.	10	0/10
Endotoxin	3 mg/100 Gm.	10	9/10
Lead Acetate (5mg./rat)	0	5	0/5
Lead Acetate (5mg./rat) + Endotoxin	1 μg/100 Gm.	12	8/12
*Slow Infusion**			
Endotoxin	1 μg/100 Gm.	5	0/5
Endotoxin	3 mg./100 Gm.	5	4/5
Lead Acetate (5 mg./rat)	0	5	0/5
Lead Acetate (5mg./rat) + Endotoxin	1 μg/100 Gm.	18	13/18

* Over 1 hour period (with a Harvard pump).

question whether a normal liver is able to clear and detoxify endotoxin from portal vein blood remains to be answered. If this process of clearance exists an approximate assessment of its inactivating capacity has yet to be made. This process was studied in the following manner.

Procedures

A close correlation between endotoxin dose and its lethality has been established in rats in both the presence and absence of lead acetate potentiation, a process first described by Selye and associates[26] and subsequently applied by Filkins.[9] Therefore we selected rats of the Sprague-Dawley strain, weighing 250–275 Gm, for our experiments. Under light ether anesthesia the abdomen was opened through a subcostal incision, and in initial experiments a small branch of the ileal vein was intubated after it was established that no intestinal infarction resulted and that the animals survived ligation of this vein. Infusion of even very small quantities of endotoxin via this route was unsuccessful because infarction of the mesenteric vein invariably occurred. The use of heparin only seemed to aggravate the problem. Hence an alternate approach was taken, as has been previously described by us for dogs.[11] The inferior vena cava was divided below the liver and the distal end anastomosed to the side of the superior mesenteric or portal vein using magnifying glasses and 7–0 sutures. This group of animals was called the reverse Eck fistula group. Intact rats served as controls.

Twenty-four hours after operation the animals were re-anesthetized and the femoral vein was cannulated. After intravenous injection of 5 mg. of lead acetate in distilled water, each animal received endotoxin (lipopolysaccharide W. *E. coli* 0.26; B6 Difco) in isotonic glucose. In some animals it was administered by rapid injection and in others by slow infusion over a period of approximately 1 hour with the aid of a Harvard infusion pump. After injection or infusion the catheter was removed and the cutdown incision closed with interrupted sutures.

TABLE 2. *Effect of Heparin (50 U) on Mortality from Endotoxin in Lead Acetate Pretreated Rats*

No. of Animals	Mode of Injection	Heparin Dose	Mortality
12	Rapid Injection	0	10/12
5	Rapid Injection	50 U	4/5
18	Slow Infusion	0	13/18
6	Slow Infusion	50 U	5/6

Results and Discussion

First we compared the difference in mortality between rapid *injection* and slow *infusion* in lead acetate pretreated, intact rats. Slow infusion was chosen since it appeared to mimic the *in vivo* development of endotoxemia more closely.

There is, as can be seen from Table 1, a slight, but not significant difference in the mortality rate between rapid injection and slow infusion of endotoxin. In this experiment the phagocytes lining the pulmonary arteries constituted the first filter encountered by the endotoxin. The findings suggest that the mortality rate is not greatly affected whether these cells are rapidly flooded with endotoxin or gradually exposed to it. This indicates that the rate of endotoxin clearance and detoxification by the cells of this filter may be very slow and allows the spilling over of endotoxin into the rest of the circulation. Histologic studies failed to reveal pulmonary abnormalities, suggesting that the lethal effect was not exerted on the lung itself.

Since slow infusion of endotoxin into freshly operated rats frequently resulted in thrombus formation at the site of the anastomosis, heparin was used to prevent clotting. Thomas *et al.*[27] and Rodriguez-Erdman[19] previously demonstrated that endotoxin activates factor XII. Hageman factor activation not only induces coagulation but as Ratnoff[17] has indicated it is associated with activation of the kinin systems and of C′ 1 esterase activity. Previous observations by Schultz and Becker[24,25] showed that heparin may activate a blood lipase system which could inactivate endotoxin through the enzymatic degradation of the lipid fraction. Hence, the effect of heparin (50 Units per rat) was studied in lead acetate pretreated intact rats.

This small dose of heparin did not cause any significant changes in mortality following endotoxin administration (Table 2) a finding at variance from that pre-

TABLE 3. *Effect of the Type of First Filter Encountered by the Endotoxin* on the Mortality Rate of Rats*

Material Infused via the Femoral Vein	1st Filter	Dose of Endotoxin	No. of Animals	Mortality	Statistical Significance
Endotoxin	Lung	3 mg./100 Gm.	10	9/10	$p < .01$
Lead Acetate (5 mg.) + Endotoxin	Lung	1 ug/100 Gm.	12	8/12	
Endotoxin	Liver	3 mg./100 Gm.	5	1/5	
Lead Acetate (5 mg.) + Endotoxin	Liver	1 ug/100 Gm.	10	0/10	$p < .0001$

* Slow infusion over 1 hour period (with a Harvard pump).

viously observed by Schultz and Becker[24,25] with larger doses of heparin.

Therefore heparin was used in the following experiment designed to study *in vivo* endotoxin clearance and inactivation by the liver. It should be noted that in the reverse Eck fistula animal the liver constitutes the first filter that encounters the highly diluted endotoxin solution while, in the intact animals the lung exerts this function. With the help of the reverse Eck fistula rats, we were able to compare the effect of the clearance and detoxifying activity of the liver, c.q. Kupffer cells, with that of the lung, c.q. pulmonary macrophages, in the group of intact rats (Fig. 1).

In contrast to the limited efficiency of pulmonary macrophages, the Kupffer cells appear to exert a very active and beneficial effect during slow infusion of endotoxin. Under these circumstances they not only seem to eliminate part or all of the minute quantities of endotoxin from blood during the first passage through the

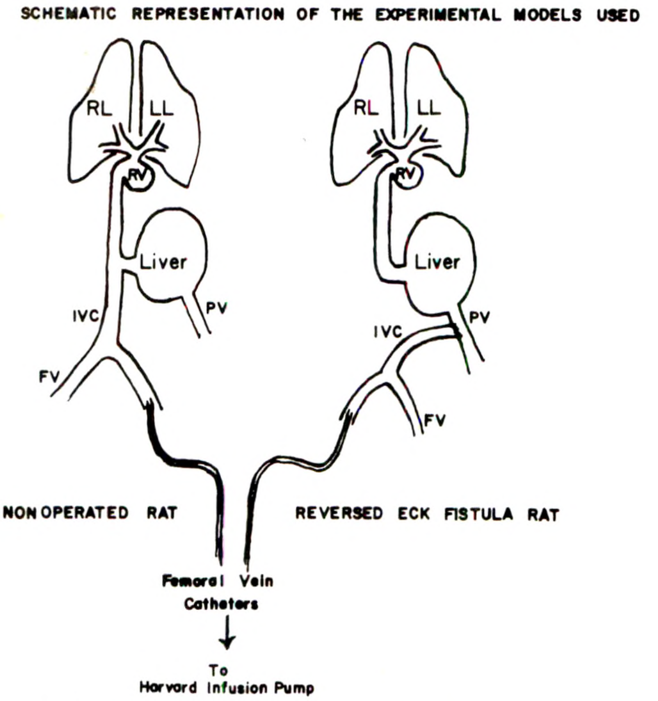

FIG. 1. Study of *in vivo* endotoxin clearance and inactivation by he liver. In the reverse Eck fistula animal (schema on the right) he liver constitutes the first filter that encounters the endotoxin nfused into the femoral vein while in the intact animal (schema n the left) the lung exerts this function. With the help of the everse Eck fistula rats we were able to compare the effect of he clearance and detoxifying activity of the liver, c.q. Kupffer ells, with that of the lung, c.q. pulmonary macrophages in the ntact rats.

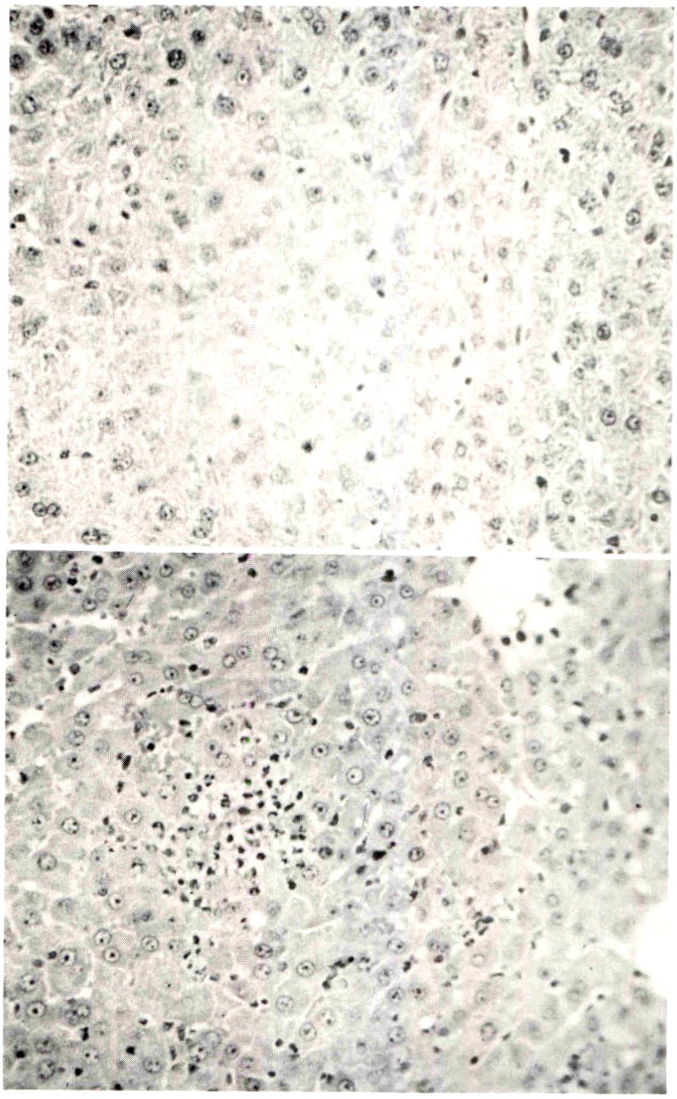

FIG. 2. Effect of endotoxin infusion on the liver was negligible in the reversed Eck fistula rats (top). In contrast focal areas of centrilobular necrosis were observed in livers of non-operated rats that succumbed to systemic infusion of endotoxin (bottom).

liver, they also are able to render a lethal dose harmless, as demonstrated by the fact that all the animals survived the 1 hour infusion of endotoxin (Table 3).

The effect of the endotoxin infusion on the liver was found to be negligible. This finding is in marked contrast to the focal areas of centrilobular necrosis observed in livers of non-operated rats that succumbed to systemic injection or infusion of endotoxin (Fig. 2). These hepatic lesions are therefore probably not endotoxin induced but are rather the result of the shock that precedes the death of these animals.

The result of this experiment would suggest that *in vivo* shunting of the liver into the perfusion circuit can protect the rat against the lethal effects of endotoxin and that Kupffer cells are much more effective in this regard than pulmonary phagocytes suggesting a specific functional difference. Whether this is due to a difference in the number of cells or to functional differentiation is presently not known. Results of studies by Howard and associates[12] would suggest that Kupffer cells are augmented and replaced by recruitment of hematogenous cells, which are probably identical with the precursors of macrophages in other areas. In view of their possible common origin, therefore it would seem that the observed difference in activity is probably not the result of morphologic or functional differentiation. An alternative explanation would be the development of a localized form of tolerance acquired by the Kupffer cells as a result of small but repeated exposures to endotoxin. This would suggest the occasional escape of endotoxin into the portal circulation, a feature for which there is presently no definite proof.

Summary

Little is known about the possible role of endotoxin in hepatic failure. It is a pertinent problem since the liver, because of its strategic location between the intestine and the systemic circulation, might well serve as a filter for endotoxin, if endotoxin is able to escape from the bowel.

If this were the case, interference with endotoxin clearance from the portal vein blood during hepatic failure, would be expected to result in development of a chronic, low grade endotoxemia.

In regard to this problem two questions arise. Is endotoxin absorbed from the gut? This is a point that remains to be settled. If endotoxin escapes, is the liver able to clear and detoxify it? The present studies carried out in rats provide evidence that the liver, in contrast to the lung, can eliminate endotoxin from blood and render it harmless.

Acknowledgment

The help of Dr. R. Dische, Dept. of Pathology, Cornell Med cal College in reviewing the histologic sections of the variou tissues is gratefully acknowledged.

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Book Review

Beyond Plastic Surgery, by CHARLES BEAVOR EDWARD, 135 pp. Wayne State University Press, Detroit, 1972. $12.95.

THIS is a small book with numerous illustrations written by a graduate of the Detroit School of Fine Arts and the Art Institute of Chicago. In addition the author is an instructor of Mortuary Science. He has had extensive experience with sculpturing and has utilized his skill in the field of prosthetics for restoration of normal body contour.

The book is highly readable, historically well documented, and the work of a person sensitive to the understanding of human physical defects. The author has done more than five hundred major prosthetic restorations and gives good general descriptions as to how to approach the restoration process. The technical descriptions would be of little interest to the surgeon but would probably serve as a guide for the budding prosthetist.

The book is of some interest to the surgeon as a source of information as to what is available. There are a number of inaccuracies by omission and some inaccurate statements about pathology and plastic surgery. In general however, I think the book bridges the gap between plastic surgery and prosthetics rather well. The author covers in detail the restoration of facial structures and in slightly lesser detail the hand, arm, thorax, and foot. As the book can be read in a very brief period of time it provides useful information to anyone concerned with restoration of body surface defects.

LINTON A. WHITAKER, M.D.

Combined Caval and Portal Hypertension with Cirrhosis of the Liver:

A Problem in Management

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DESPITE the postoperative metabolic problems so frequently encountered and the increased risk of major operative procedures in patients with liver disease, a well constructed portal-systemic shunt offers the best available protection against recurrent bleeding from esophageal varices.[7,10,11,12]

Most patients who bleed from esophageal varices usually have portal pressures in excess of 300 mm. of water.[9,14] Normal inferior vena caval pressures range between 30 and 50 mm. of water varying with respiration, position and cardiac function. The success of the portal-systemic shunt in the control of subsequent bleeding from esophageal varices depends on the large pressure differential between the congested portal circulation and the normal systemic circulation. All of these operations shunt blood from the splanchnic circulation to the inferior vena cava below the liver.

This report discusses two cases in which the construction of a portacaval shunt in patients with cirrhosis of the liver and bleeding esophageal varices was unsuccessful because of striking elevation in inferior vena caval pressure. Retrohepatic compression from a hypertrophied and nodular caudate lobe caused the caval hypertension in both instances.

Case Reports

Case 1. W. C. G. was a 50-year-old man with a history of heavy ingestion of alcohol over many years. He entered the Manchester Veterans Administration Hospital with massive hematemesis, ascites and physical findings and laboratory studies consistent with Laennec's cirrhosis of the liver. The initial bleeding episode was managed with blood replacement and intravenous vasopressin. During the subsequent month he was prepared for elective portal-systemic shunt with a diuretic program and restoration of nutrition.

At laparotomy the free portal pressure was 325 mm. of water and the occluded hepatic portal pressure 300 mm. of water. All pressure measurements were recorded with #19 gauge needle and glass tube manometer connected by intravenous tubing. An end-to-side portacaval shunt was selected rather than a side-to-side shunt due to an hypertrophied caudate lobe. At the conclusion of the shunt the portal pressure had dropped only 40 mm. of water. Neither technical stricture nor angulation of the portal vein could account for this unsatisfactory drop in pressure. Inferior vena cava pressure was recorded at 285 mm. of water and concurrently a superior vena cava pressure was 100 mm. of water. No technical maneuver to rectify this situation was immediately apparent. The patient had a massive gastrointestinal hemorrhage on the tenth postoperative day and died.

At post-mortem examination regenerating nodules in the caudate lobe were found narrowing the lumen of the inferior cava to 5 mm. Retrohepatic obstruction of the vena cava was apparently responsible for the caval hypertension.

Case 2. N. E. was a 40-year-old man with a long history of alcohol ingestion. He was admitted to the Manchester Veterans Administration Hospital with massive upper gastrointestinal bleeding and physical findings and laboratory studies consistent with Laennec's cirrhosis. Because of persistent massive bleeding, a Sengstaken-Blakemore tube was inflated and he was transfused to restore normal blood volume.

At laparotomy on the following day, the free portal pressure was 380 mm. and an hepatic occluded portal pressure was 350 mm. of water. A pressure was recorded in the inferior vena cava as 260 mm. of water. It was not felt to be technically feasible to

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resect the entire caudate lobe. No other solution to avoid the problem of anastomosing two high pressure systems was apparent. Therefore, an end-to-side portacaval shunt was performed. Upper gastrointestinal hemorrhage recurred on the first postoperative day resulting in profound hepatic coma. The patient died on the third postoperative day.

At post-mortem examination the diameter of the retrohepatic vena cava was narrowed to 7 mm. by large regenerating nodules in a cirrhotic caudate lobe.

Discussion

The construction of a satisfactory portacaval shunt between the splanchnic and caval systems below the liver usually results in a marked drop in portal pressure. Most reported series[3,6,7,10,12] indicate that this type of decompression has resulted in a low incidence of recurrent bleeding from esophageal varices. In the two cases described, obstruction in the retrohepatic vena cava resulted in caval hypertension with pressure similar to those found in the splanchnic circulation. The resulting decompression through portacaval shunting was minimal. Recurrent variceal hemorrhage caused death in both patients indicating inadequate portal decompression.

Figure 1 illustrates the anatomical location as seen in both autopsies and the mechanism by which this type of retrohepatic caval compression causes hypertension in the inferior vena cava. A typical Budd-Chiari syndrome was not present in these two cases because the compression was below the entrance of the right and left hepatic veins.

These cases call attention to vena caval hypertension which appears to preclude the chance of a successful portal decompression through standard shunting procedures. The incidence of caval hypertension is not known since, to our knowledge, there are no previous similar case reports. The existence of this syndrome, however, might indicate that caval pressures should be measured prior to operation. If the pressure is significantly elevated in the inferior vena cava (greater than 250 mm. of water), other procedures such as portal-azygous disconnection as described by Tanner,[13] transthoracic ligation of esophageal varices,[1,4] or the transthoracic transposition of the spleen[15] might prove to be a more satisfactory solution to this complicated hemodynamic problem.

Summary

The incidence of rebleeding from esophageal varices is lowest following satisfactory portal-systemic shunts. Retrohepatic vena cava obstruction and subsequent infrahepatic caval hypertension precludes a successful portal-systemic shunt.

This report discusses two cases in which regenerating nodules in a cirrhotic caudate lobe caused significant retrohepatic vena cava obstruction. Preoperative pressure measurements of the infrahepatic and suprahepatic vena cava could document this obstruction and if found another surgical approach to this problem would be indicated.

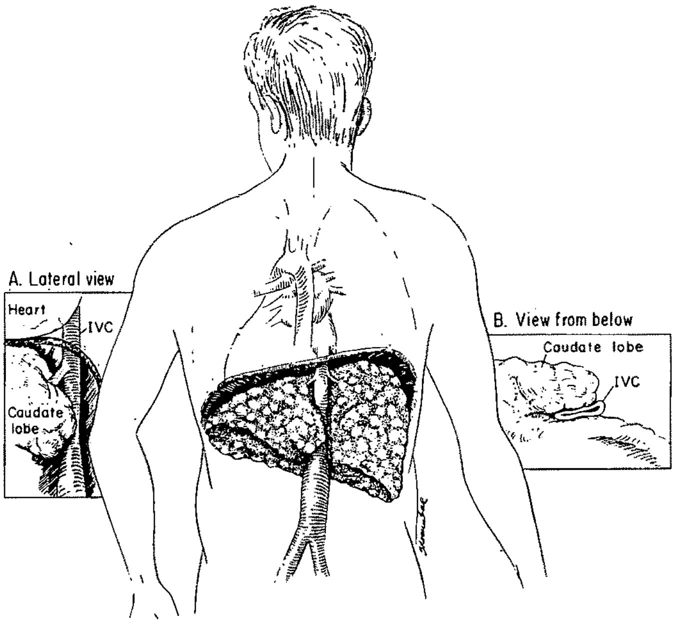

FIG. 1. Illustrates the anatomical location of the retrohepatic inferior vena cava compression in a lateral, inferior and posterior projection.

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Book Review

Renal Transplantation Theory and Practice, by J. HAMBURGER, J. CROSNIER, J. DORMONT, and J-F BACH. Williams and Wilkins Company, Baltimore, 1972, 326 pp.

THIS book reviews the spectrum of problems in renal transplantation from basic transplantation immunology, through numerous clinical aspects of transplantation, to important secondary considerations such as psychological, moral, and legal problems. The text is well organized and every important aspect of transplantation has been covered. Translation from French into the English version has been expertly accomplished by A. Walsh in collaboration with the authors. Every one working in the field should gain from reading the smoothly flowing text, but it will be particularly valuable to residents and fellows still in training because of its concise overview of the subject. Coming from the Hôspital Necker in Paris, it is not surprising that the book is more oriented toward the European literature and accomplishments of European investigators than are most reviews published in this country. It should also be noted that while the authors usually present opposing views in areas of controversy, a certain amount of dogmatic bias remains in the text. As an example, the authors state without qualification that a catheter must be left in place for at least 8 days if the bladder has been opened. Our unit would certainly take exception to such a statement since we have not seen complications with routine removal of the catheter between 24 and 36 hours. Numerous other points in protocol differ from the experience in other transplant centers, but represent honest opinion based on personal experience in a rapidly moving field where guidelines are still unstable. In all, the book is superior, if not outstanding, and will be a welcome text to newcomers entering the field.

J. WESLEY ALEXANDER, M.D.
Department of Surgery
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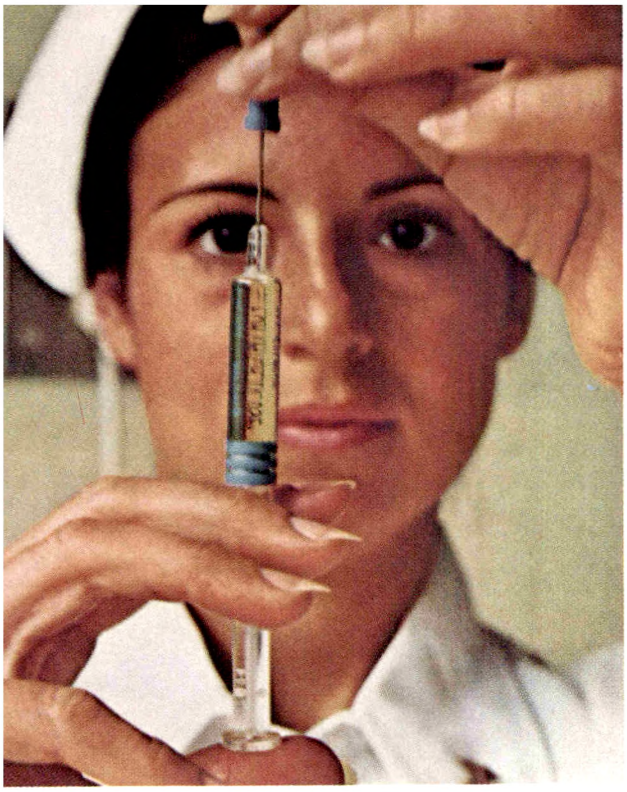

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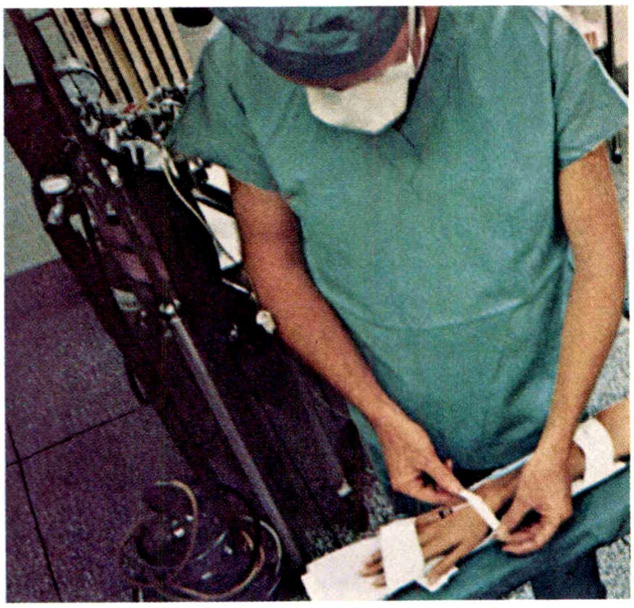

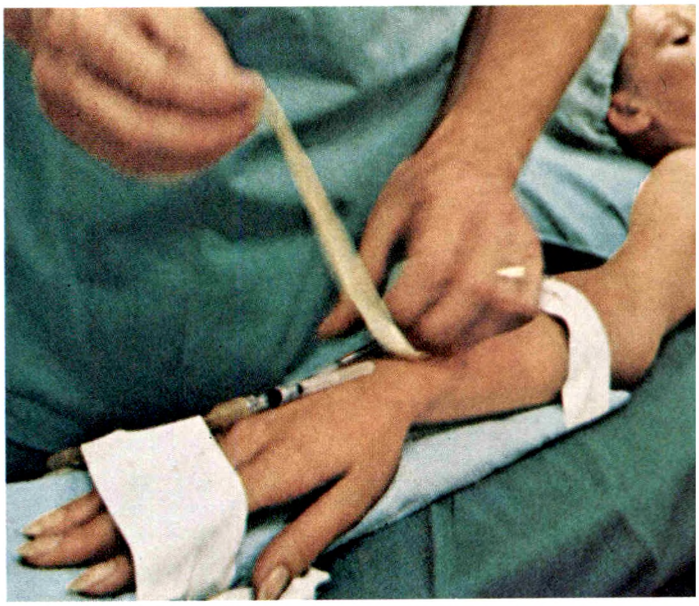

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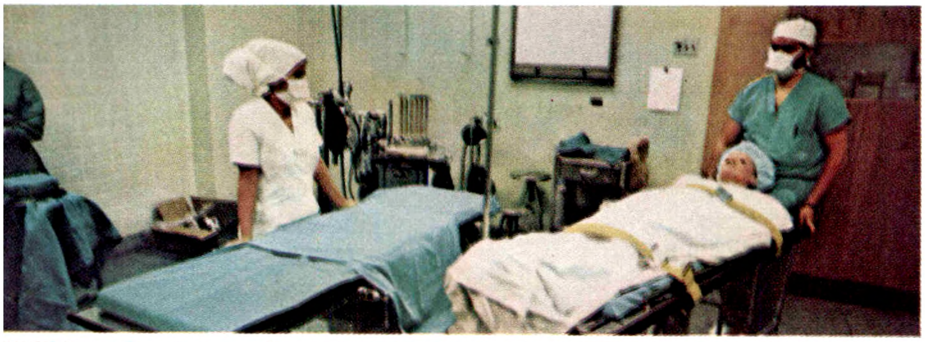

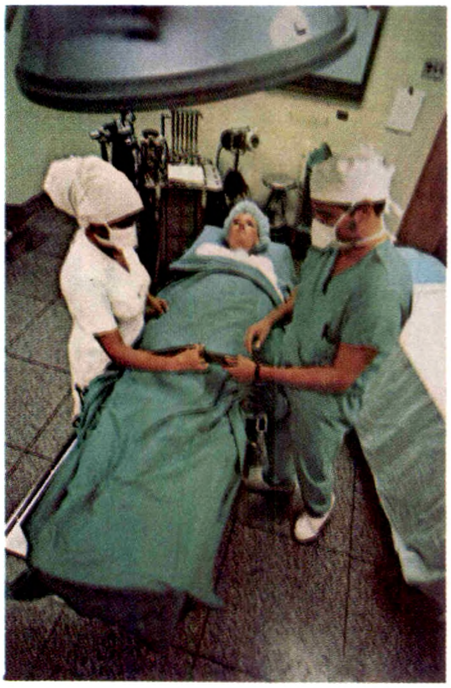

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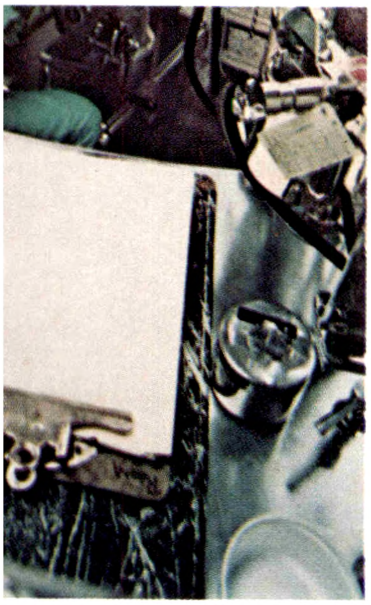

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Usage in ambulatory patients: Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using Percodan should be cautioned accordingly.

Interaction with other central nervous system depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Percodan may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Percodan should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children: Percodan should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS: *Head injury and increased intracranial pressure:* The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of Percodan or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients: Percodan should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS: The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea and vomiting. Some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. The usual adult dose is one tablet every six hours as needed for pain.

DRUG INTERACTIONS: The CNS depressant effects of Percodan may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the effect of uricosuric agents.

MANAGEMENT OF OVERDOSAGE: *Signs and Symptoms:* Serious overdose with Percodan is characterized by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of Percodan may, in addition, result in acute salicylate intoxication.

Treatment: Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

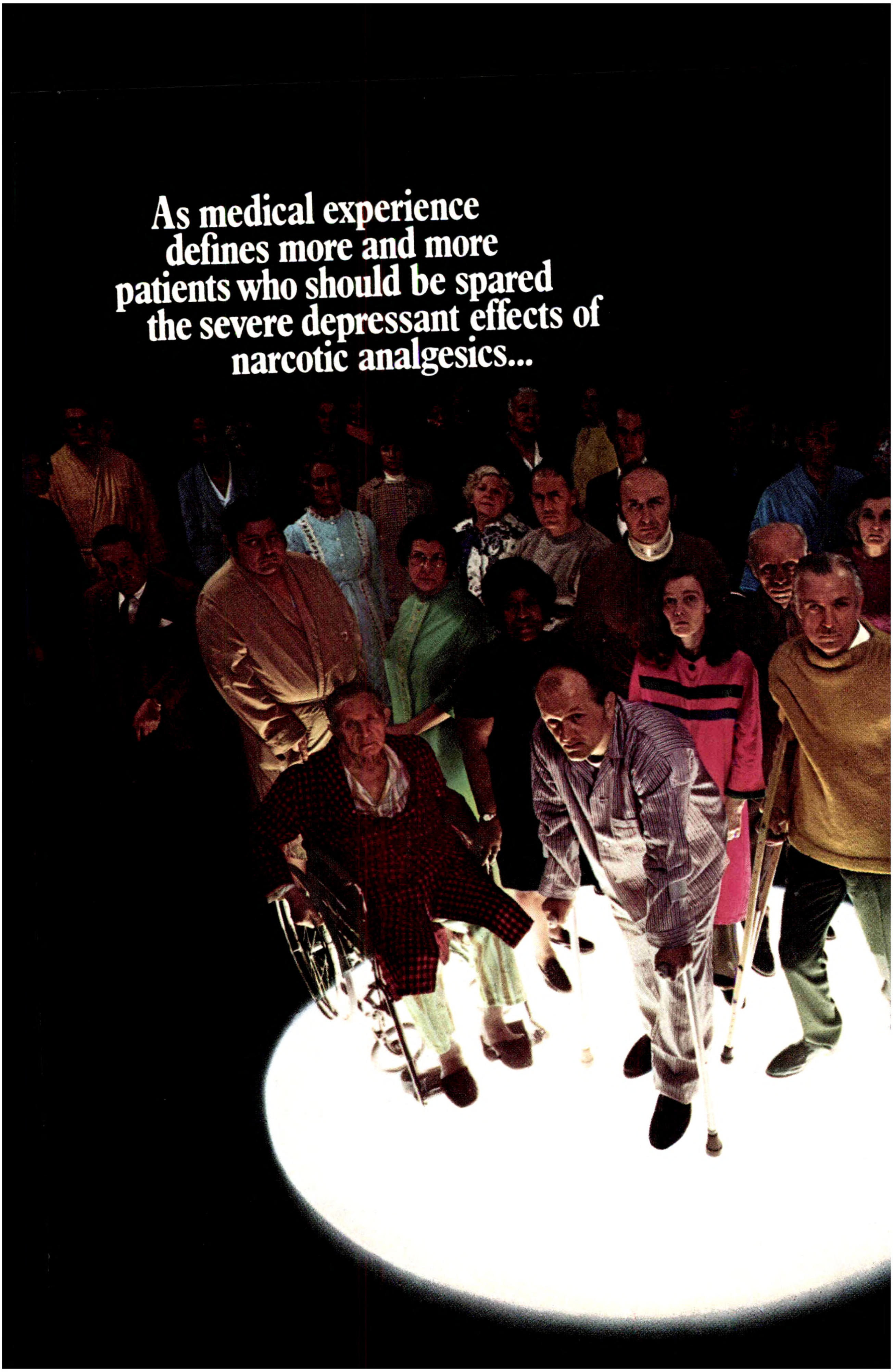
When pain is moderate
to moderately severe

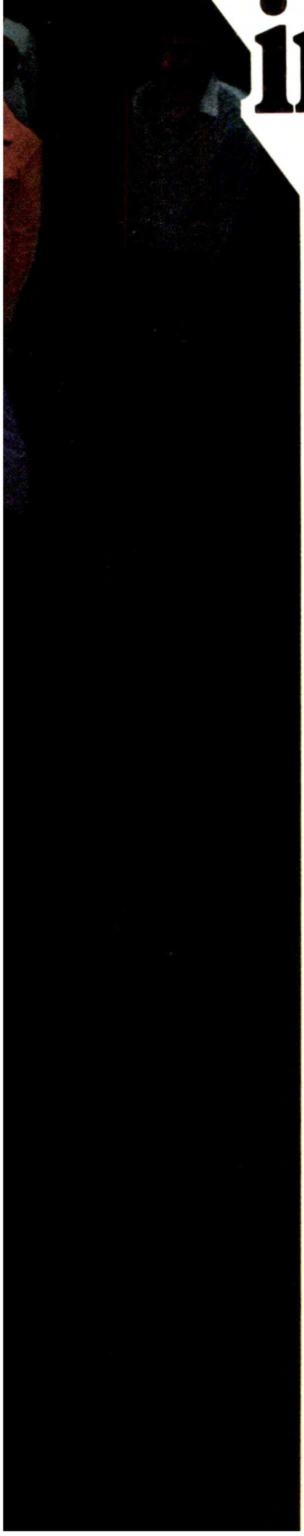
Percodan Ⓒ II

Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit-forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit-forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

reliable, rapid relief

Endo Laboratories, Inc.
Subsidiary of E I du Pont de Nemours & Co. (Inc.)
Garden City, N Y 11530
DU PONT


As medical experience
defines more and more
patients who should be spared
the severe depressant effects of
narcotic analgesics...



The Pain Population in need of Injectable Talwin® Brand of pentazocine (as lactate) is growing

When circumstances call for a potent analgesic, vulnerability to the depressant effects (circulatory, respiratory, urinary) of narcotics may be increased:

in patients with

- chronic illness
- advanced age
- chronic obstructive lung disease
- pleural effusion
- cirrhosis
- myocardial infarction
- prostatic hypertrophy

in patients who have had

- general anesthesia
- considerable blood loss
- muscle relaxants for surgery

...and in many other patients

when depression of respiration, circulation, or urinary retention should be minimized.

Talwin® provides analgesic efficacy comparable to that of morphine and meperidine, but with fewer significant adverse effects:

Compared to morphine, Talwin causes less severe respiratory depression, hypotension, urinary retention, constipation.

Talwin is less likely to cause nausea, vomiting, diaphoresis than meperidine.

Tolerance to analgesic effect has not been reported.

Not subject to narcotic controls.

See next page for a discussion of warnings, precautions, adverse reactions and other Prescribing Information.

Injectable
Talwin®
Brand of pentazocine (as lactate)

in moderate to severe pain

Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Available in 30mg., 45mg., and 60mg. strengths:

little, if any, increase in incidence or severity of adverse reactions reported with increased doses of 45 mg. or 60 mg.

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindications: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Head Injury and Increased Intracranial Pressure.* The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously receiving narcotics have experienced mild withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *other:* tachycardia, soft tissue induration, nodules, cutaneous depression, and ulceration (sloughing) at the injection site, weakness or faintness, chills, moderate transient eosinophilia, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, midlateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist. If naloxone is not available, parenteral administration of the analeptic, methylphenidate (Ritalin®), may be of value if respiratory depression occurs.

Talwin is not subject to narcotic controls.

How Supplied: *Ampuls of 1 ml. (30 mg.) and 1½ ml. (45 mg.)* in boxes of 10, 25, and 100. *Ampuls of 2 ml (60 mg.)* in boxes of 25 and 100. Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

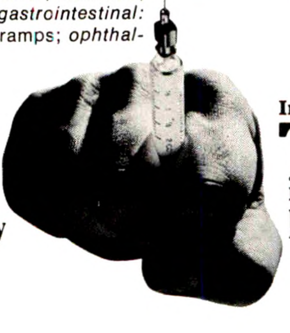
Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Winthrop Laboratories, New York, N.Y. 10016

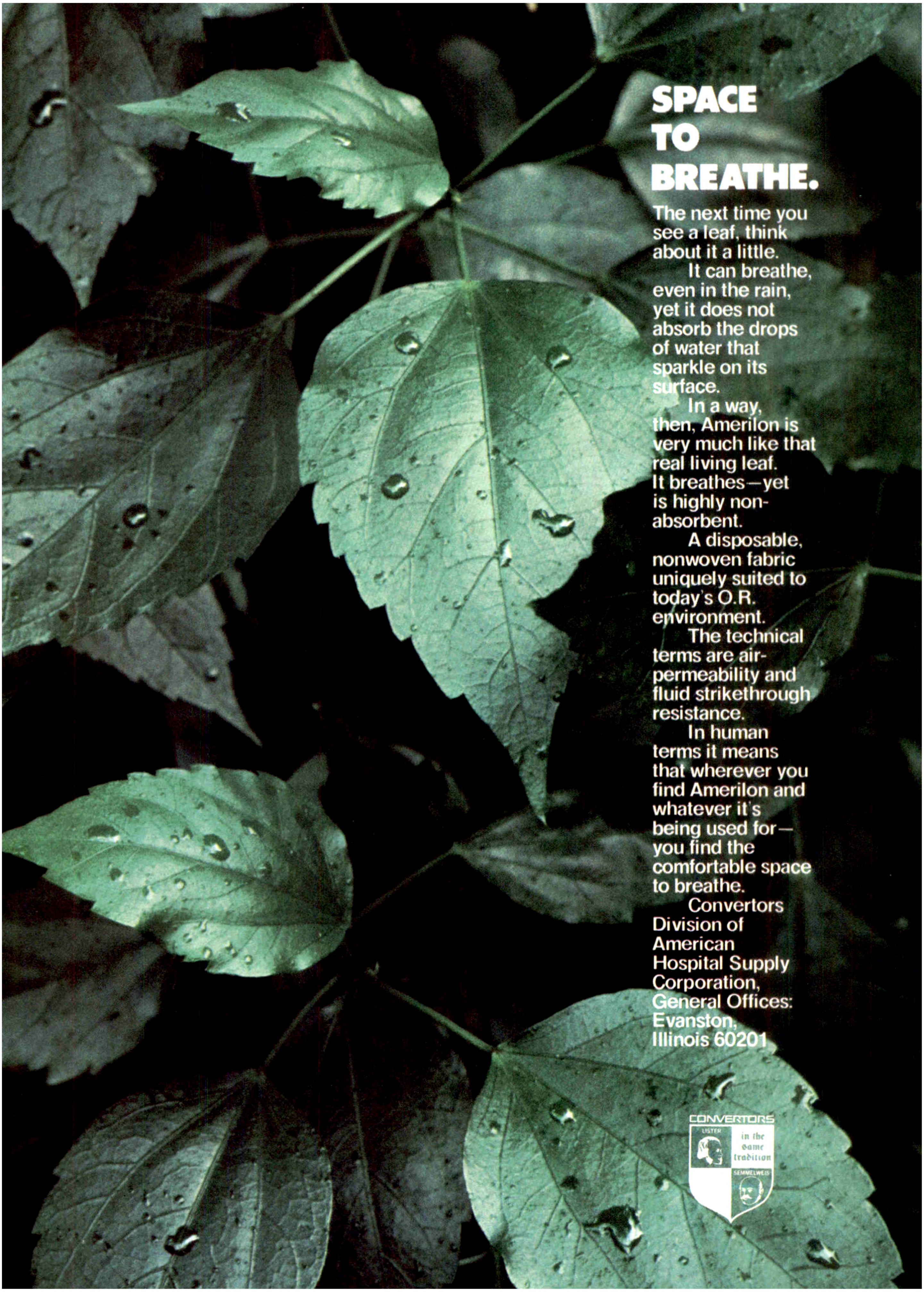
Winthrop

bulwark against pain
of moderate to severe intensity



Injectable
Talwin®
Brand of
pentazocine
(as lactate)

(1593)



SPACE TO BREATHE.

The next time you see a leaf, think about it a little.

It can breathe, even in the rain, yet it does not absorb the drops of water that sparkle on its surface.

In a way, then, Amerilon is very much like that real living leaf. It breathes—yet is highly non-absorbent.

A disposable, nonwoven fabric uniquely suited to today's O.R. environment.

The technical terms are air-permeability and fluid strikethrough resistance.

In human terms it means that wherever you find Amerilon and whatever it's being used for—you find the comfortable space to breathe.

Convertors
Division of
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Hospital Supply
Corporation,
General Offices:
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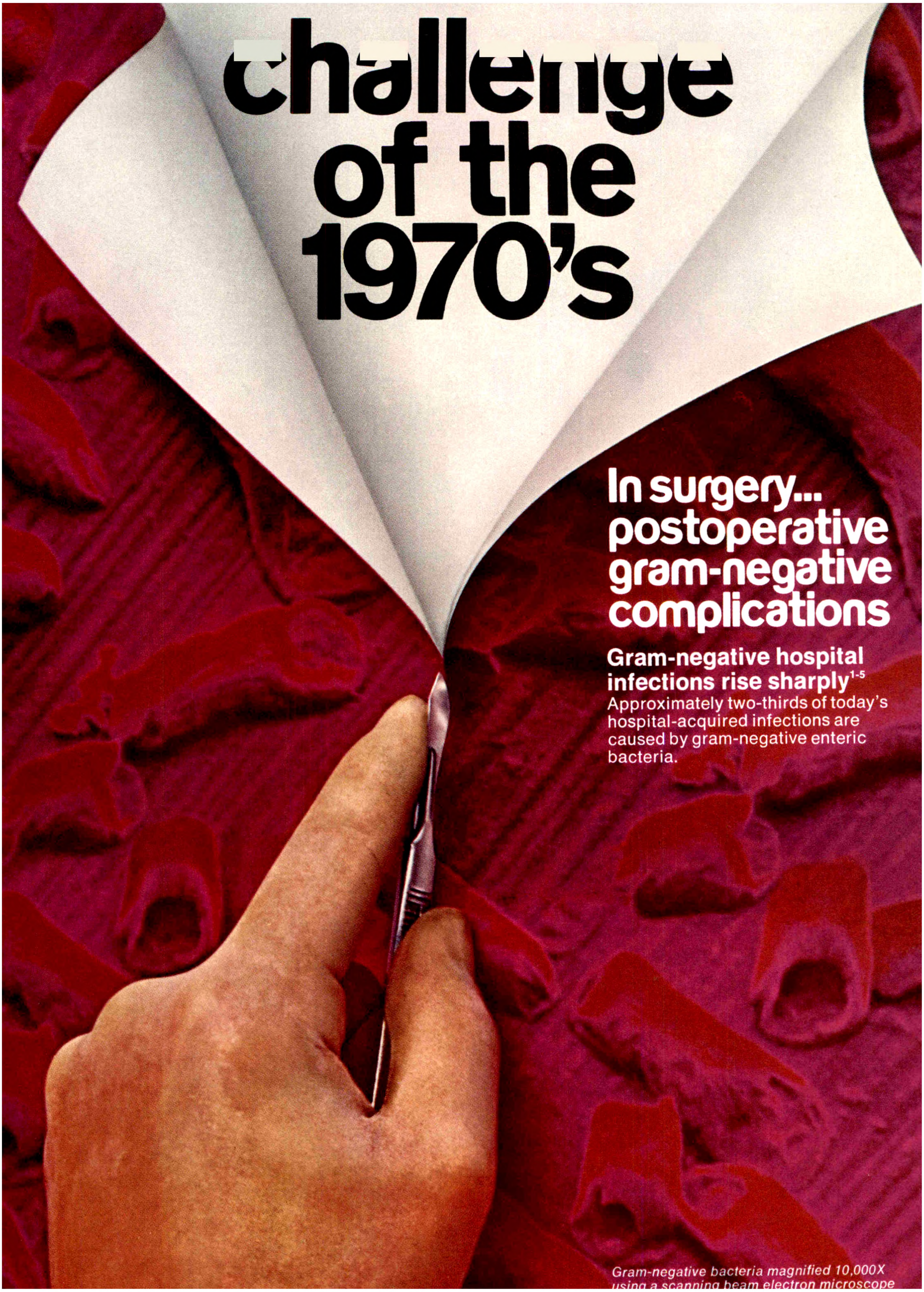
Illinois 60201

CONVERTORS
LISTER
in the same tradition
SEMMELWEIS



challenge of the 1970's

In surgery... postoperative gram-negative complications

Gram-negative hospital infections rise sharply[1-5]

Approximately two-thirds of today's hospital-acquired infections are caused by gram-negative enteric bacteria.

Gram-negative bacteria magnified 10,000X using a scanning beam electron microscope

Schering

antibiotic of the 1970's

Antibiotic of FIRST resort

In suspected or documented gram-negative sepsis, GARAMYCIN Injectable may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important concepts contained in the Warning Box.

GARAMYCIN Injectable is effective against today's problem pathogens[6-9]

GARAMYCIN Injectable offers an almost indispensable antibacterial spectrum for today's gram-negative infections. It has a high probability of effectiveness against virtually all of the gram-negative pathogens implicated in serious surgical infections.*

Proven clinical efficacy[7,10-19]

GARAMYCIN Injectable usually produces a dramatic response in wounds and burns complicated by sepsis...and may be lifesaving in septicemia.

Although studies demonstrating clinical effectiveness were not conducted on postoperative patients, GARAMYCIN Injectable has also shown outstanding results in serious gram-negative respiratory infections and is strikingly effective in selected urinary tract infections.

Relatively low incidence of adverse reactions

The risk of toxic reactions is relatively low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended. For patients with impaired renal function, see Package Insert for full prescribing information.

Bacteria remain highly sensitive

In a survey of published studies on resistance to gentamicin, Weinstein and co-workers[20] report little change in bacterial sensitivity since 1963. The percentage of sensitive strains of virtually all gram-negative pathogens remains high.

In serious postoperative infections

Garamycin®

gentamicin sulfate injectable

I.M./I.V.

40 mg. per cc.

Each cc. contains gentamicin sulfate equivalent to 40 mg. gentamicin

---

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

in serious postoperative infections... get the 24-hour head start with

Garamycin® Injectable
brand of gentamicin sulfate U.S.P., injection, 40 mg./cc.
Each cc. contains gentamicin sulfate equivalent to 40 mg. gentamicin
For Parenteral Administration

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USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms: **Pseudomonas aeruginosa, Proteus** species (indole-positive and indole-negative), **Escherichia coli** and **Klebsiella-Enterobacter-Serratia** species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin type drug is usually indicated as concomitant antimicrobial therapy.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

Schering

DOSAGE AND ADMINISTRATION GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:

PATIENTS WITH NORMAL RENAL FUNCTION*

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb.), the usual dosage is 80 mg. (2 cc.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dose is 60 mg. (1.5 cc.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

*In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration, in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 cc. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution, in both instances should normally not exceed 1 mg./cc. (0.1%). The solution is infused over a period of 1 to 2 hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically pre-mixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per cc., 2 cc. multiple-dose vials for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per cc., 2 cc. multiple-dose vials for parenteral administration. APRIL, 1972
AHFS Category 8:12.28

For more complete prescribing details, consult Package Insert or Physicians' Desk Reference. Schering literature is also available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

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SLR-317R

Garamycin®
gentamicin sulfate
injectable
I.M./I.V.
40 mg. per cc.
Each cc. contains gentamicin sulfate equivalent to 40 mg. gentamicin

15%–20% price reduction*

Keflex®

cephalexin monohydrate

now costs less*

*On the basis of price reduction by Eli Lilly and Company to distributors.

Reductions vary by dosage form. Reductions on Identi-Dose® (unit dose medication, Lilly) packages are 13%-14%.

Lilly

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Additional information available to the profession on request.

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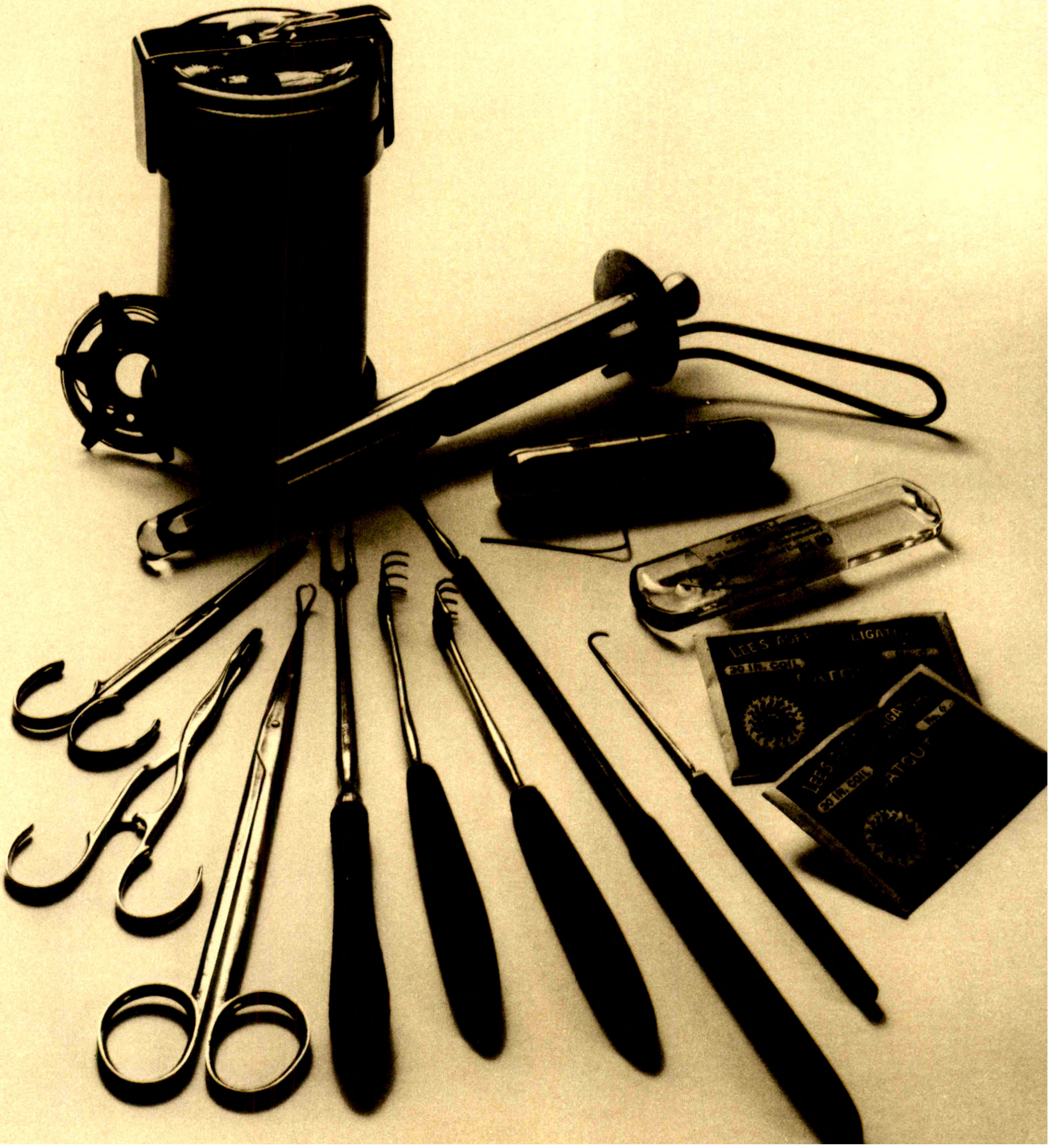
Three good reasons for using catgut yesterday:

1. The only absorbable suture available.
2. Familiarity with its handling properties.
3. Limited failures with it.



Eight good reasons for using DEXON® polyglycolic acid suture today:

1. Supple, silk-like hand.
2. Knot security—tied securely, it holds securely.
3. High tensile strength—minimizes breaking.
4. Sustained strength through the critical wound healing period.
5. No fraying.
6. Predictable absorption, even in contaminated areas.
7. Minimal tissue reaction and inflammatory response.
8. Improved patient comfort.

See next page for complete product information.

The future is with
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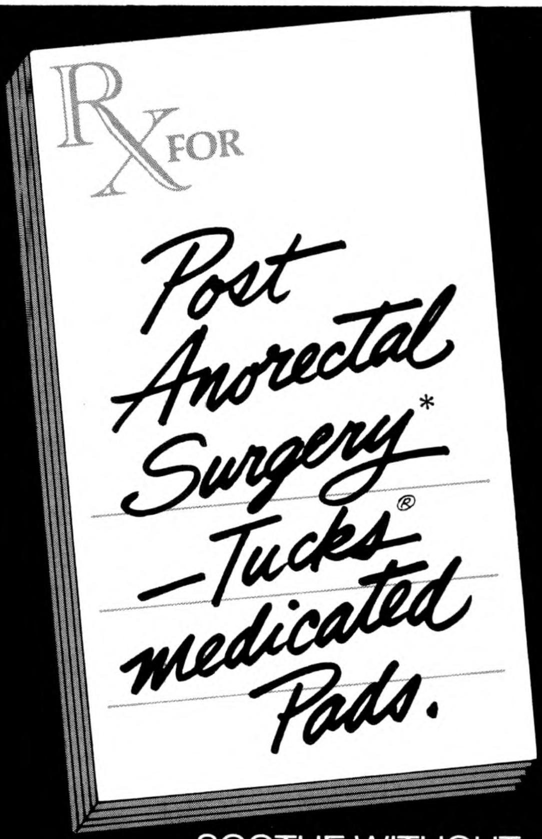

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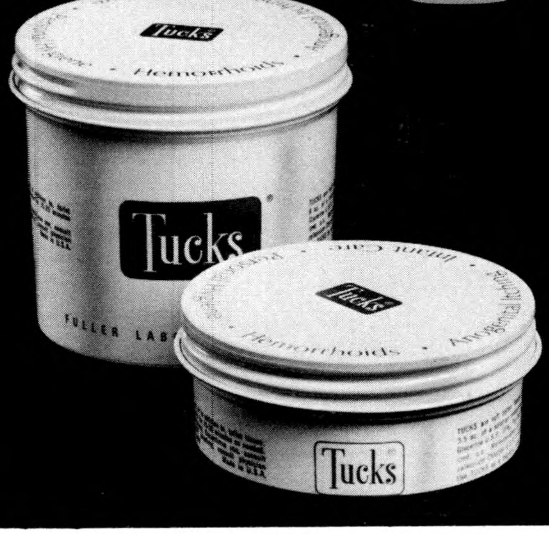

Early Treatment of War Wounds of the Hand and Forearm in Vietnam

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> *"There is a close relation between the early and late phases of treatment. The surgeon who deals with these wounds at the battlefront, giving them their first definitive treatment, in large measure predetermines the course of events."*
>
> LTC. C. W. CUTLER, JR., 1945[13]

THE VIETNAM WAR has provided to yet another generation of American surgeons the opportunity of learning first-hand the technics of combat surgery. In the past 7 years many arduously-learned principles of wound care have been reaffirmed.[4,9,11] In addition, the rapid evacuation of casualties by rotary-winged aircraft from relatively fixed geographic areas of combat to stationary medical facilities has created an unprecedented opportunity for surgeons to carry out procedures and achieve results not possible in earlier wars. As a consequence of this orderly and immediate flow of patients from combat to hospitals in Vietnam and finally to the United States, the correlation between immediate care and the ultimate result is probably closer than it has ever been before.

The authors served at the 3rd Field Hospital, Vietnam, between May, 1969 and October, 1970 and treated the majority of patients with hand and forearm wounds admitted to that hospital. The purpose of the present report is to document the technics employed during that period in the immediate management of wounds of the upper extremity, emphasizing those procedures serving to simplify or shorten the future course of reconstruction.

Clinical Data

The records of 147 patients with hand and/or forearm wounds were reviewed. All patients were injured in combat and were transported by helicopter directly to the 3rd Field Hospital. Patients who could be treated in the hospital's emergency room with local anesthesia were excluded from the report. The time interval from wounding to operation ranged from less than 1 hour to as much as 6-8 hours, but rarely more. Longer delays, when present, were usually due to the inability of helicopters to enter areas of active combat to evacuate casualties.

Table 1 lists the wounding agents and reflects the character of the Vietnam War during the period of study. The high number of fragment and blast wounds (73%) illustrates the enemy's reliance on booby traps, rockets, and satchel charges as weapons and agrees generally with other published studies.[25]

Wounds were separated into three general catagories: 1) *Gunshot wounds*—the result of one or more high velocity missiles (greater than 2,000 feet per second) usually fired from the AK-47, the Communist equivalent of the United States model M-16; 2) *Fragment wounds*—the result of high velocity metallic fragments from a device such as a grenade, mortar round, or rocket. Identification of the specific weapon was usually impossible; 3) *"Blast" wounds*—the result of the concussive effect of an explosive device, such as a land mine or "plastic". Such injuries are characterized by multiple wounds with heavy tatooing by dirt and debris.

Associated injuries to other organ systems were frequent (Tables 2 and 3). Three deaths occurred in the series and all resulted from massive trauma to multiple

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The views expressed herein are solely those of the authors and should not be construed as representing policy of the United States Army.

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TABLE 1. *Mechanism of Injury in 147 Patients*

Mechanism	Number	Per Cent
Multiple Fragment Wounds	90	61
Gunshot Wounds	36	25
Blast	18	12
Unknown	3	2

systems. Management of the extremity wounds was at times dictated by the presence of other injuries.

Table 4 indicates the frequency of injury to various anatomic structures in the hand and forearm. Nerves which were nonfunctional at preoperative examination were reported as injured even if they were anatomically intact at operation. Muscles were listed as injured only if it was felt that the amount lost through wounding and debridement would significantly reduce their function. Tendons were included if they were completely divided.

Table 5 is a listing of the procedures preformed both on the day of wounding and at subsequent operations. All procedures were performed at the 3rd Field Hospital.

Patient follow-up was necessarily short due to the policy of rapid aero-medical evacuation from Vietnam. As a general rule, patients remained at the 3rd Field Hospital for 8–12 days, *i.e.*, until a delayed primary closure of their wounds could be performed and a 3–5 day observation period allowed to elapse. Unusually heavy casualty loads occasionally necessitated earlier evacuation. In accordance with official policy, a patient remained at the 3rd Field Hospital for a mandatory 14-day period if an arterial repair was performed. The majority of patients, therefore, were evacuated from Vietnam 8 to 14 days following wounding. Wounds in this series were treated with the expectation that the surgeon performing the initial operation would have the opportunity of reoperating on the patient. One hundred and twenty-four patients actually underwent a second procedure at the 3rd Field Hospital. Of the remaining 23 patients, a primary closure was performed in three instances, and 20 others were evacuated prior to further operation.

Operative Procedures

The choice of anesthesia was based on the patient's injuries and general condition. Axillary or supraclavicular block, general anesthesia, or intravenous lidocaine were utilized at various times. A pneumatic tourniquet was available in all instances and was usually employed for some portion of the procedure.

TABLE 2. *Location of Wounds in 147 Patients*

	Patients	Per Cent
Limited to Upper Extremity	72	49%
Other Areas or Organ Systems	75	51%

TABLE 3. *Wounds Involving other Major Areas in 75 Patients—51% of Total*

Area of Wound	Number	Per Cent of Multiply-Wounded	Per Cent of All Patients
Lower Extremity	45	62	31
Abdomen	19	26	13
Head and Neck	17	23	12
Back	14	18	10
Chest	10	13	7
Genitalia, Perineum	6	8	4

Initial Surgery: Wounds were scrubbed with soap and a surgical brush and copiously irrigated with saline (Fig. 1-A). The importance of this procedure in the reduction of contamination and prevention of infection cannot be over-emphasized. All wounds were then surgically debrided. Except for tangential wounds, it was rarely necessary to debride more than a few millimeters of skin and subsequent wound closure usually posed no problem. Muscle debridement frequently had to be wide and the amount necessary was sometimes difficult to gauge. Bone was not removed unless completely detached from all soft tissue. Frayed tendon ends were trimmed smooth. Hematomas were treated aggressively by wide decompression, evacuation, and drainage. Arteries in the vicinity of wounds were explored and repairs were performed when indicated. Major nerves in the vicinity of wounds were visually inspected and their condition carefully noted. Divided nerves were minimally debrided. Fasciotomies were performed over the flexor and extensor muscle groups of the forearm, the dorsal interossei, and the lumbrical muscles of the hand. The volar carpal ligament was divided if necessary (Fig. 1-B). At the completion of these procedures hemostasis was carefully obtained by ligature and cautery. Fine mesh gauze, absorbable sponges, and a supportive plaster splint were applied and the extremity was elevated continuously until the time of the second procedure.

Reparative Surgery: The surgeon's judgment and the logistical situation determined when this phase of treatment was begun. In the absence of infection or other complications, the patient was usually returned to the operating room 3 to 5 days after injury (Fig. 1-C). At that time further debridement could be carried out if necessary. Definitive alignment and fixation of fractures was also performed. Kirschner wire fixation was the method of choice in hand and wrist fractures, but only external splinting was used for the forearm. In metacarpal fractures without loss of bone substance, fixation was accomplished by crossed wires or by a transverse wire through the metacarpal heads and a vertical wire in the medullary canal to prevent angulation.

The problems associated with loss of bone substance and shortening of the bony framework are all well known to surgeons involved in the late reconstructive surgery of war wounds. In patients with significant loss of metacarpal length, a special effort was made to stabilize distal bone fragments to intact adjacent bones or to use Kirschner wire "spacers" to maintain length. This practice has greatly simplified subsequent bone-grafting and reconstruction (Fig. 2).

Phalangeal fractures were usually treated with crossed or multiple small Kirschner wires, inserted in standard fashion. A number of patients had all or parts of one or more fingers amputated. Particular care was taken to preserve viable innervated skin in such cases for use in later coverage. In addition, badly damaged fingers were saved if future use of remaining parts seemed likely.[8]

Wound closure was by direct suture, autograft,[12] or local flaps fashioned from the skin of a filleted finger. Homografts were occasionally used for temporary wound coverage. Flaps and skin grafts were left exposed postoperatively to permit frequent observation. Patients were evacuated from Vietnam 3 to 5 days after wound closure if their condition was satisfactory (Fig. 1-D).

Discussion

A large majority of our patients had sustained high velocity missile wounds. The pathophysiology of these wounds has been well-described and is beyond the scope of this report,[1,15,16,18,24] but it should be emphasized that such wounds characteristically produce marked destruction at great distances from the missile track and are frequently accompanied by massive contamination. For these reasons, they do not lend themselves to the technics employed in the treatment of wounds incurred in civilian life.

War surgeons have appreciated the importance of the early management in the subsequent course of upper extremity wounds.[2,3,4,5,23] In 1944, Churchill identified three stages in the treatment of war wounds: initial surgery, reparative surgery, and reconstructive surgery.[9] This classification has been modified to fit the particular circumstances of the Vietnam War. The term *initial surgery* refers to procedures carried out within a few hours of wounding and is primarily directed toward preservation of life and limb. Its purpose in the hand and forearm is to preserve and protect all remaining vital structures and prepare them for reparative surgery. Churchill noted that *reparative surgery* "is designed to prevent or cut short wound infection . . . and is performed between four and ten days, 'the golden period' to close wounds, reduce and fix fractures, remove retained missiles, and carry out other procedures to prevent or abort infection." *Reconstructive surgery,* such as nerve suture, tendon repair, bone grafts, and pedicle flap coverage, was not performed in Vietnam.

TABLE 4. *Injured Structures, Upper Extremity in 147 Patients*

Structure		Number of Patients		Per Cent	
Bone		93		63	
	Hand		70		48
	Forearm		23		15
Nerve		60		41	
	Hand		38		26
	Forearm		22		15
Muscle		49		33	
Tendon		45		31	
Artery		15		10	
	Wrist-Elbow		10		7
	Elbow or Above		5		3

TABLE 5. *Surgical Procedures—Immediate or Delayed in 147 Patients*

Wound Closure	127	
Immediate Suture		3
Delayed Suture		112
Autograft		12
K-Wire Fixation of Fracture		53
K-Wire Spacer for Bone Loss		10
Amputation		23
Evacuation of Hematoma		15
Arterial Repair	15	
Saphenous Vein Graft		4
End-To-End		4
Lateral Suture		3
Ligation		4
Fillet of Finger		6
Decompression	76	
Forearm Fasciotomy		47
Intrinisic Muscle Fasciotomy		17
Volar Carpal Ligament Division		12

In previous wars, the initial operation was carried out near the front, whereas reparative surgery was performed at base hospitals located to the rear. In Vietnam, however, there is no front and the terms, "forward" and "rear" are anachronistic; and it is not uncommon for the initial operation and subsequent reparative work

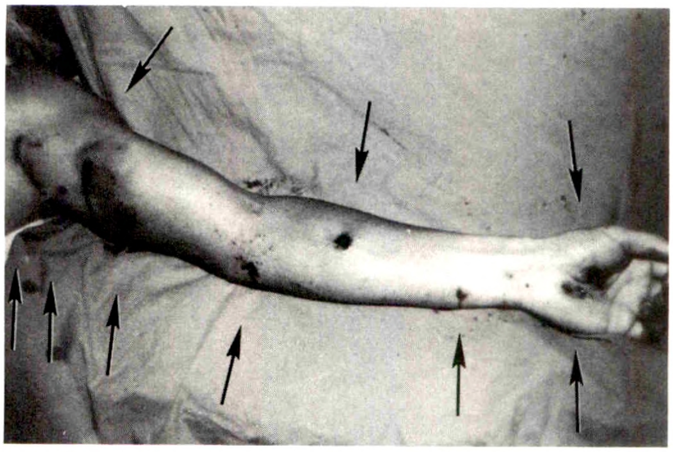


FIG. 1-A. Day of injury. There are multiple fragment wounds. (arrows) Division of brachial and radial arteries, median nerve division, ulnar nerve contusion, fractures of humeral epicondyle and 3rd metacarpal. Wounds will be debrided, arteries repaired, volar carpal ligament excised.

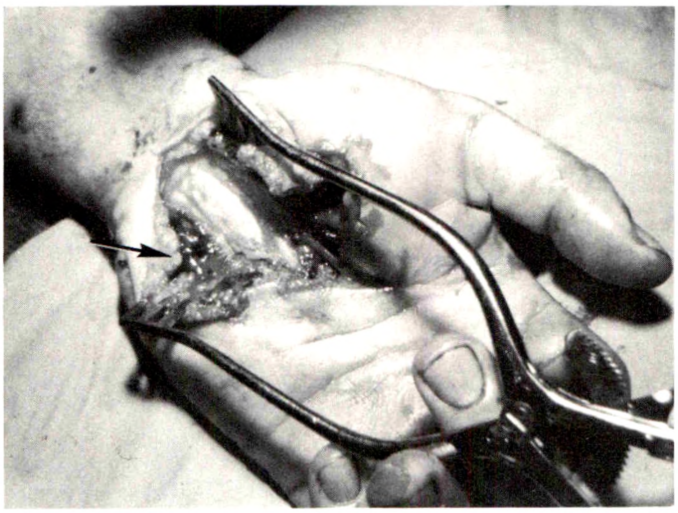


FIG. 1-B. Day of injury. Closeup of hand showing volar carpal ligament excision. Note hematoma (arrow) over ulnar aspect of ligament.

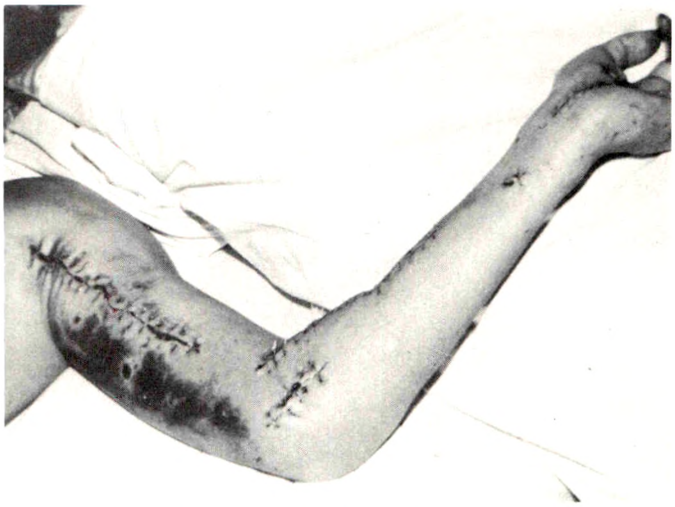


FIG. 1-D. Fourteen days after wounding. Wounds are healing without infection, pulses are present. Note resolving hematoma, upper arm. The patient was evacuated to Japan.

to be carried out at the same hospital and by the same surgeon. This modification in approach to the treatment of war wounds is possible for two reasons: 1) hospitals are stationary and secure and 2) the helicopter and jet transport provide a degree of patient mobility which has not been possible in previous wars.

The staged approach to wound management limits the initial operation to those procedures necessary to 1) restore viability 2) relieve the pressure of hematoma or edema 3) remove non-viable or heavily contaminated tissue and foreign bodies, 4) and inspect nerves or arteries to determine the presence and degree of injury.

At the time of initial operation first priority is assigned to the repair of arterial injuries. The presence of such injuries frequently is suggested by a large hematoma or bright red bleeding, but damage to a vessel may sometimes be present in the absence of these signs. All major vessels in the vicinity of a wound should be inspected, even if a pulse is present distal to the wound.

Injury to an artery may result in either thrombosis (secondary to intimal damage), partial division, or complete division. Resection of the damaged segment and direct anastomosis usually can be performed without difficulty in the first two instances. A completely divided vessel, however, may be best managed by resecting the damaged ends and inserting a saphenous vein graft. This technic allows a tension-free repair and avoids the necessity of dividing collateral branches to gain length.

The large scale repair of vascular injuries by hun-

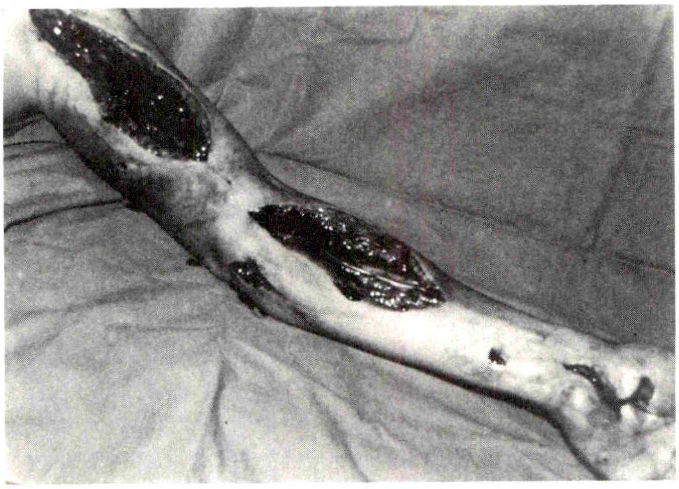


FIG. 1-C. Five days after wounding. Hand is viable, wounds are open, clean, uninfected. Ideal for fracture fixation and wound closure.

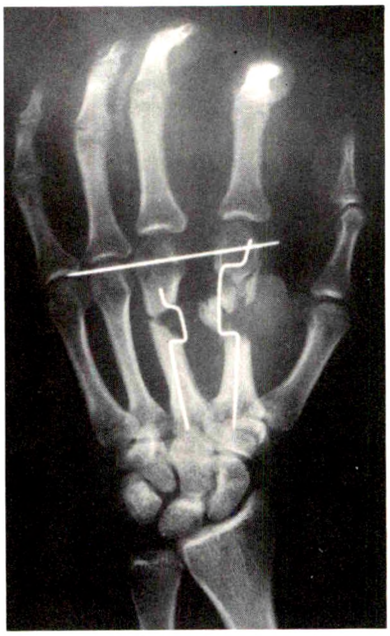


FIG. 2-A. Two months after gunshot wound with comminution and partial loss of second and third metacarpals, extensor tendon loss. Kirschner wire spacers and transverse wire are in position to maintain length.

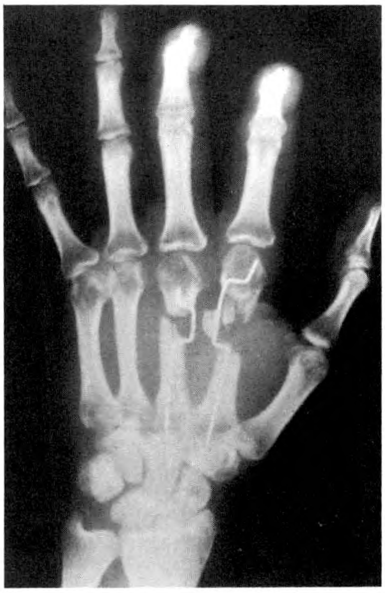


FIG. 2-B. Three and a half months following wounding. Note slight collapse of third metacarpal head following removal of transverse wire.

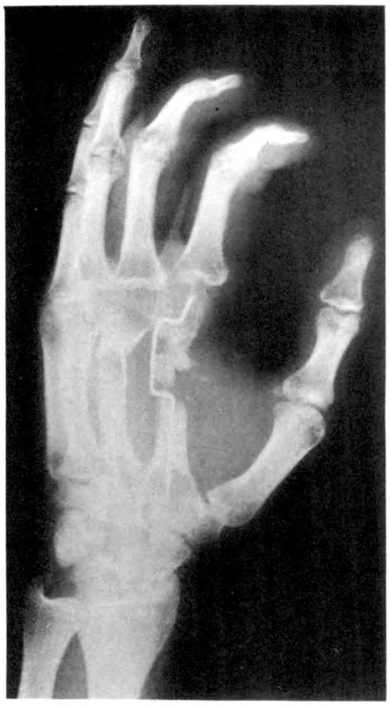


FIG. 2-C. Three and a half months. Oblique view showing absence of union —ready for iliac crest bone grafting.

dreds of surgeons has been a major advance in the care of the wounded in Vietnam. Survival and amputation rates have been consistently better than those obtained n other wars.[14,17,25,26] Early thrombosis of saphenous vein grafts in the upper extremity has sometimes been a source of disappointment however.[7] Although the magnitude of injury clearly plays a major role in such failures, it is felt that scrupulous attention to technic may minimize such complications. Particular care must be taken to distend the vein graft with a dilute heparin solution and to dissect away constricting areas of adventitia to make certain that there are no areas of narrowing. Of the 11 arterial repairs performed above the wrist, five were at the elbow or higher and involved the brachial artery. These extremities were potentially nonviable. Four of the patients required saphenous vein grafts, three being at the elbow and one in the upper arm. There was no loss of limb and pulses were present distal to all repairs fourteen days later when the patient was evacuated.

Table 5 illustrates the emphasis placed on decompressive procedures. In addition to standard forearm flexor and extensor fasciotomy, intrinsic muscle fasciotomy and volar carpal ligament division were frequently performed for wounds or edema of the hand and wrist. Burkhalter *et al.*,[6] have emphasized the value of these procedures in reducing the pressure on intrinsic blood upply, minimizing median nerve compression, and facilitating tendon motion through the carpal tunnel.

Although fasciotomy has been widely advocated for he leg, upper arm, and forearm, fascial releases in the hand have not been stressed adequately. These procedures seem to offer many advantages, are simple, and an be carried out quickly and with little morbidity. Hopefully, they will be employed more frequently in the future.

Amputations were performed at the initial procedure only when the part in question was clearly nonviable. Only one amputation was performed at the carpal level and none proximally. No complications were noted to result when marginally vascularized flaps of skin were

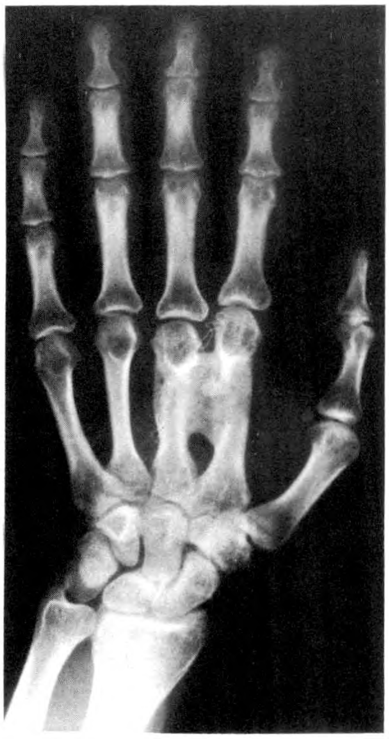
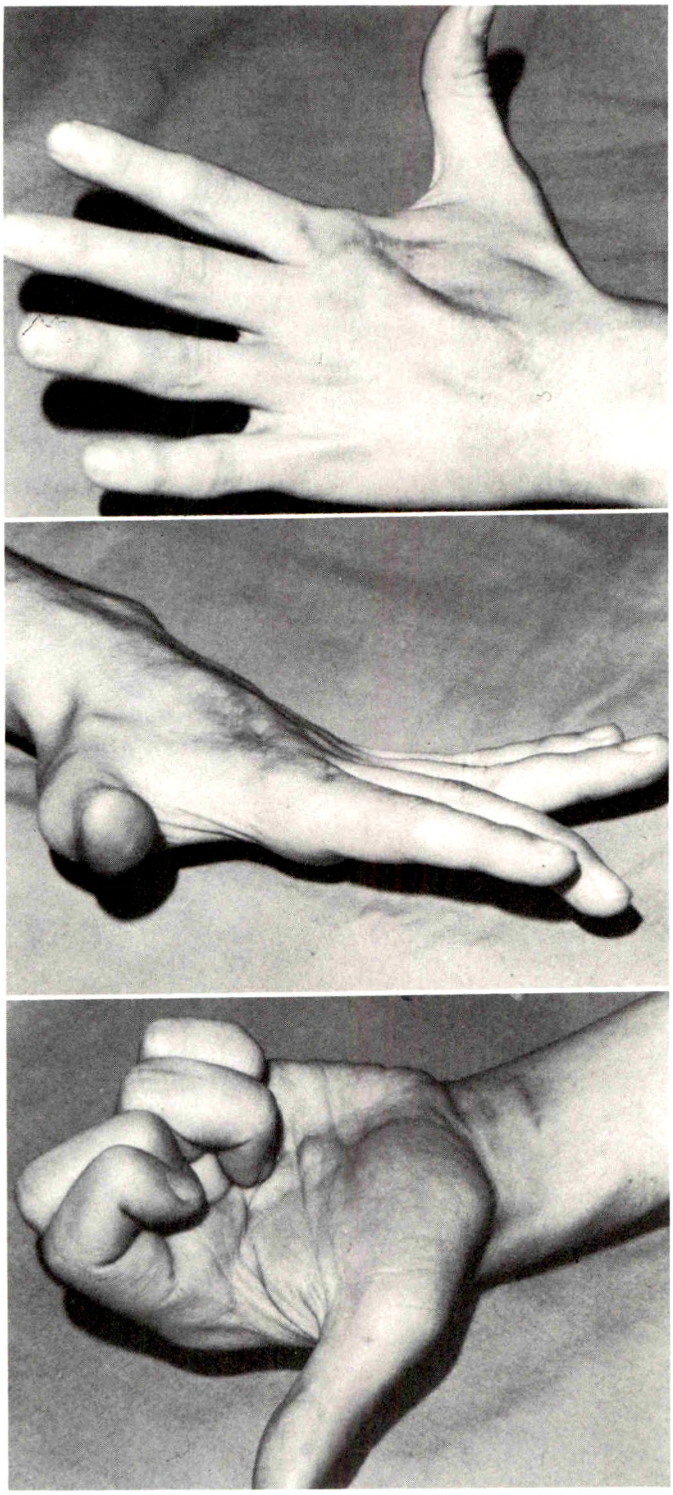


FIG. 2-D. Fourteen months after wounding, bone graft is healed. Extensor tendon transfer and graft has been performed to index and middle fingers respectively (note small wires).



FIGS. 2-E, F, G. Final result, showing appearance of wound, range of motion. 45° flexion and full extension is present at MP joints.

allowed to remain at the first operation, since a second chance to debride them was available. This technic resulted in greater skin salvage.

The initial stage of surgery was always terminated with irrigation and a search for bleeding vessels. The importance of hemostasis is not diminished by the fact that wounds are to be left open. Hematoma and bleeding have produced many wound complications in Vietnam which might have been avoided by more careful hemostasis.

Decisions regarding the use of antibiotics are still largely empiric. The majority or patients wounded in Vietnam are given antibiotics when first seen by a physician. Many of our patients, however, did not receive antibiotics, particularly if there were no associated injuries. Only one patient in this series developed a clinical infection, a rate of 0.68%, and this occurred despite treatment with antibiotics. This success seems to substantiate the philosophy of Mason's excellent discourse on the treatment of open wounds.[20] Infection is prevented by faithful adherence to surgical principles, not bacteriological principles.

There are several advantages to the two-stage method of wound management: 1) A more conservative debridement can be performed at the time of initial operation since the operator knows there will be a second opportunity to remove tissue of questionable viability. 2) Hematomas which accumulate in the wound following initial operation can be evacuated. 3) Time-consuming procedures such as fracture fixation can be performed at a time when the patient's condition is generally more stable than at the time of initial resuscitation and treatment. 4) Wounds are not closed over nonviable or minimally viable tissue. 5) Wound closure is performed at a time when edema is beginning to subside.

There exist differences of opinion concerning the relative merits of primary and delayed primary closure of hand wounds. We have chosen not to distinguish between these two methods but to emphasize that both are *primary*, so long as closure is performed within 4 to 7 days of wounding. There is no evidence suggesting an advantage to closure on the day of injury or a disadvantage to closure within 7 days of wounding. Healing occurs at virtually the same rate, and the final result is unchanged.[19,27] It is the responsibility of the surgeon to "close the wound when it is ready for closure" and this should be done at the earliest possible date. It may occasionally be on the day of injury but a vast experience with high velocity war wounds has shown that wound closure can be more safely performed at a later date. Wound severity notwithstanding, many of the most difficult problems seen in military hospitals in the United States are the result of wounds which have been closed only to disrupt at a later date because of infection, tension, or closure of tissue with marginal circulation. The major issue which thus evolves is not *when* the wound is closed but that once closed it *stay closed* and heal without infection.

The immediate care of war wounds of the hand has changed considerably in America's last three wars. For most of World War II, the initial surgical treatment of wounds was followed by open treatment. A delayed closure was performed as the patient moved to the rear. As armies advanced and evacuation chains lengthened, however, hand and forearm wounds sometimes remained open for 2 to 4 weeks or longer. This regimen produced infection, stiffness, and fibrosis and resulted in the recommendation that primary closure of hand wounds be attempted. Immediate closure was in fact practiced in the later stages of World War II and initial results were encouraging in a limited series, but several instances of wound breakdown and life-threatening infection were seen.[10] No final conclusions could be drawn at that time about its efficacy. Following World War II and during the Korean War, there was continued interest in immediate reconstruction. McCormack[22] in 1959 pointed out the improved capability of hospitals and surgeons and suggested that immediate reconstruction be performed on selected cases. Mason and Bell,[21] in that same year, advocated "primary closure if at all feasible" but cautioned that "extensive reparative surgery in a hand already badly handicapped by the original trauma may wreck the patient's only chance for a functioning hand. The surgeon must remember that *unless primary healing can be secured*, the later reparative surgery may be unduly delayed and difficult, and may produce a poorer result. Bunnell stated that "the goal of all initial wound care is to obtain healing by first intention with a minimum of tissue reaction." To this we would add, at the earliest possible time and whatever means necessary.

Summary

1. A group of 147 war wounds of the hand and forearm from the Vietnam War is presented.
2. The staged approach, utilizing early débridement followed by reparative procedures and delayed primary closure, is advocated.
3. The more frequent use of intrinsic muscle fasciotomy and volar carpal ligament is recommended.
4. Emphasis is placed on the relationship between proper initial treatment and the ultimate success of reconstruction.

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Gunshot Wounds of the Abdomen

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THIS IS A CONTINUING serial study of civilian gunshot wounds of the abdomen as seen in a large metropolitan hospital over a 40-year period. It began in 1930–1938 and indicated a startling 52.8 per cent mortality for all perforations of the abdominal cavity.[4] When an abdominal viscus had been injured, 60 per cent died. To present day standards this is unbelievable and yet these were average figures of the period.

From that time to the present, similar studies were made in the Marion County General Hospital covering the periods 1938–1946,[5] and 1955–1962.[2] The present report presents the experience for 1962–1970. It is noted that no analysis was made during the years 1946–1955. Including this undocumented period there were some 700 patients operated upon at our hospital for gunshot wounds of the abdomen, 1930–1970.

A word might be said about our "gunshot" clientele. Nearly two-thirds were Negro in a city in which blacks constitute one quarter of the population. As might be expected two-thirds of all patients were in their young active years, 18 to 35. In the early years of the study practically all were charity patients. Presently, many are subscribers to health insurance.

The Marion County General Hospital is a large city hospital into which which many patients are channeled who are injured in auto accidents and practically all who sustain gunshot wounds. It is a teaching hospital associated with Indiana University School of Medicine. It is staffed by interns, residents and a voluntary staff which in recent years is partly replaced by a full time staff. Throughout this 40-year period, although the staff has changed, those in charge have been well trained, qualified and dedicated in the field of trauma and violence.

There are few examples which illustrate recent surgical progress so dramatically as that seen in the treatment of gunshot wounds of the abdomen. The decrease in the expected mortality to one fifth during four decades is startling and gives cause for reflection and analysis of this progress. The over-all picture is briefly indicated in Table 1. A 60 per cent rate of mortality through a relatively short period of 40 years has been reduced to 12.7 per cent.

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Also shown are the percentage of negative explorations for abdominal gunshot wounds which have remained relatively constant. No excuses are offered for these incorrect diagnoses. We expect them in the future and feel that this level of "mistakes" should be maintained. If allowed to drop to a lower level it is our belief that the death rate would rise above the present enviable figures. During the four periods reported there were 92 negative exploratory operations. In these periods there was but one operative death. Autopsy findings failed to indicate a cause.

The hospital's policy is to perform immediate laparotomy unless it can be definitely shown that the bullet did not enter the abdominal cavity. Watchful waiting suggested by some is not advocated.[6] Beneath the innocent cutaneous puncture mark may lie damage requiring the utmost skill to attempt a repair. We have not used opaque media and x-ray to determine penetration of the abdomen but have resorted to judgment as to course of the bullet, clinical findings and occasionally local exploration of the tract. A period of observation in stab wounds has been useful but rarely in gunshot wounds.

During the last 8-year study there were 39 negative explorations in 246 laparotomies. The injuries of six patients which were observed without operation proved to be tangential wounds and two shotgun wounds with a diffuse pellet pattern which were also successfully observed. To complete this most recent group of un-

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operated patients there were three who had central nervous damage precluding and overshadowing all thought of abdominal exploration. These patients were omitted from analysis since the abdominal wound was not the deciding factor. Patients who died before admittance to the hospital were excluded from study.

Also indicated (Table 1 and Fig. 1) is a distressing feature of modern American life. After a brief decline during the World War II years, gun-play on our streets has spiraled and is increasing at a very rapid rate. It is not known what part of all civilian gunshot wounds occur in the abdomen but it is assumed that this percentage by chance remains constant and is representative. The escalation of violence has been noted by others[3,6,7] with no indication of control. Only the care and treatment affects the medical profession but certainly this violence is cause for worry and serious concern.

Table 2 analyzes the mortality rate resulting from various organ injuries through the four periods. In our earlier reports and as noted by others, multiple viscus injuries are prone to carry an increased mortality rate. This feature is unexplainably absent in the most recent group.

It was interesting to find that in the years 1962 to 1970, deaths from injuries of the stomach and/or small intestine dropped to less than 3%. This represented one death in 42 patients caused by a shotgun blast at close range with death occurring in the operating room.

We are beginning to save a few patients with injury to the great vessels. During the first two series these patients never reached the operating room. As noted less than half of ten patients survived following injuries of the aorta, renal artery or portal vein. In 21 injuries to the iliacs or vena cava since 1955 there were six deaths. This indicates progress but it is not expected to improve much more nor to be as dramatic as the improvement after injuries of other viscera. Vascular injuries require a tremendous amount of transfused blood at operation. The average was 7.2 units per case and the maximum given was 25 units.

There has been considerable discussion among members of the department as to whether or not all colon injuries and repairs should have a diverting colostomy at the time of exploration. The procedures used and results obtained are listed for the most recent study (Table 3). Although the numbers are small it would seem that uncomplicated wounds to the colon can safely be closed primarily and that many complicated colon injuries may safely receive the same treatment. Also indicated is the fact that extremely severe injuries definitely should have primary colostomies with or without exteriorization of the injured segment but that there will be a sizeable mortality in such cases despite this procedure. On the basis of such cases we are in agreement with the Houston series,[1] believing that each situation must be individualized.

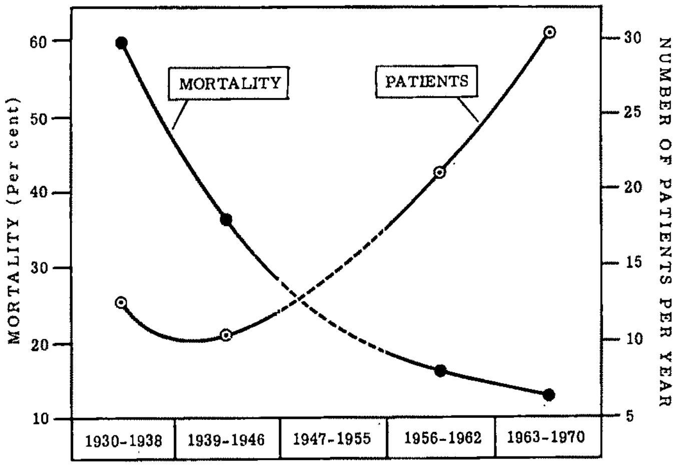

FIG. 1. Graphic representation mortality and incidence of gunshot wounds of the abdomen.

TABLE 2. *Mortality Per Cent Resulting from Various Injured Organ*

	1930–1938	1938–1946	1946–1955	1955–1962	1962–1970
Stomach-Small	45.	0	—	15	2.38
Colon-Rectum	33.	33.	—	0	11.8
Gut + Solid Viscus	84.	70.	—	36	11.9
Solid Viscus	70.	5.3	—	13.	11.1
Great Vessel—					
Aorta, Renal A.					
Portal V.	—	—	—	75	62.
Iliacs, Vena Cava	—	—	—	45.	20

Shotgun injuries have not been compared with other

TABLE 1. *Overall Results—574 Surgically treated Patients*

	1930–1938	1938–1946	1946–1955	1955–1962	1962–1970
Mortality with					
Visceral Injury	59.8%	36.2%	—	16%	12.7%
Neg. Explorations	14.%	21.4%	—	17.5%	15%
Pts. Explored	101.	84.	—	148	241

TABLE 3. *Colon Injury 1962–1970*

	Primary Closure	Colostomy or Exteriorization
Colon Injury Only	3 cases All lived	4 cases All lived
Colon Injury + Other Viscera	13 cases 1 died	43 cases 6 died

bullet wounds of the abdomen as they are a thing apart. If inflicted at a distance where they produce a diffuse spattered pattern they are often benign and the patient may be observed. However, at close range they are as lethal as a cannon, removing all tissue in their path. During the most recent study there were 13 shotgun wounds with ten operations and three deaths. Three were safely observed.

It is surprising that approximately 20% of the patients in the last series had self inflicted wounds. Of these instances it is impossible to determine those patients with suicidal intent since the history often changed after admission.

A word might be said about high velocity gunfire in comparison with the usual low velocity bullet in our civilian injuries. The occasional wound inflicted by a high velocity missile left its unmistakable telltale mark of great tissue damage. Our statistics would be far less favorable had these weapons predominated.

During the last 246 explorations there were at least two overlooked perforations which eventually lead to death. This is a tragedy but perhaps can not be entirely prevented since an overly long and tedious search at operation may also add to the risk.

Annalysis of Improved Mortality

No single feature stands out above all others as being responsible for this gratifying salvage of patients with abdominal gunshot wounds. We find instead a number of improvements along the 40-year span which when taken singly are only moderate innovations, but added together they have provided significant advances.

First of all the manner of managing patients has changed completely. In the early days the staff doctor was alerted at all hours to help with or actually perform the operation. This routine was used before the 4-year residency period. At the present time the fourth year resident who has had more experience with cases of abdominal trauma than the average staff doctor, handles it well and competently. He merely notifies his staff and proceeds with the necessary treatment. Often when the great vessels are involved there is no time for even this procedure. Chests and abdomens have been opened in the emergency room in an attempt to control hemorrhage. These heroics will continue to yield only a small salvage rate although none of these patients were saved before.

Next in importance is the introduction and continued use of the naso-gastric suction tube. Strange as it now seems, this procedure was not used at all during the first reported period. The remarkable improvement indicated in the second period (1938–46) must in great part be due to a flat abdomen and deflated gut which provided a better physiological situation to effect wound healing and sustain life by postoperative naso-gastric suction.

Third in importance must be knowledge of electrolyte balance and gas exchange. The latter has come into clinical use only during the most recent study and the former received little consideration during the first periods of study. The assessment of both values are now considered vital to the management of any gunshot wound. In this connection the amount of blood given preoperatively during consecutive periods is interesting. This amounted to an average of 20 ml. per patient during the first period; had increased to 580 ml. for the next 8 years; 1250 ml. for the third period and decreased to 875 ml. for the most recent years. The decline is not due to lack of appreciation of this colloid but the realization that in the early stages, dextran or Ringer's lactate can be safely substituted for blood. The above figures exclude the amount of blood that was given to patients with great vessel injuries.

Antibiotic agents are considered by many to be the most important factor in the survival of these patients. This is an argued point. Antibiotic agents were not available during the first two periods of the continuing study and yet one of the most remarkable improvements in the mortability rate occurred between the first and second periods. Unfortunately every patient in the most recent study received antibiotic agents in huge amounts. There were no controls who received none. During the third period study (1955–1962) antibiotic agents which were used in most patients but not all. This provided no important differential.

It is our personal opinion that the administration of antibiotic agents are of little use in controlling general peritonitis or abdominal abscess. They can be of inestimable value in combatting the complications of pneumonia, pylephlebitis and pylelitis, which may be deciding factors of life or death. They should be administered but indiscriminate use may not affect the primary abdominal contamination. Reliance on drugs must never be substituted for good surgical treatment.

Lastly, much credit for recent improvements in mortality rates must be given to the anesthesia department. Our patients are in competent hands throughout the operative care and later in the intensive care units. There has been considerable advancement from the old methods of open drop ether given by an available intern or medical student.

It has not been the purpose of this paper to report the details of operative procedure or gut repair which have been adequately described many times. Technical details vary moderately at other institutions and while arguments may arise from such disagreements, they are of little consequence in the overall picture. Technical changes of operation in our own institution have varied little in the past 40 years but there has been a vast change in the modern overall care of patients. It is to this factor that we direct attention.

Addendum

Recently there have been several spurious reports advocating lavage of the contaminated general peritoneal cavity with saline alone or mixed with antibiotic agents. May it be stated that the remarkable improvement indicated in the present review was achieved without this practice.

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Contamination of the Wound during Operation and Postoperative Wound Infection

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BACTERIOLOGICAL examination of the surgical wound during operation may have two important functions, *viz.* for tracing the sources of wound infection, and for selecting groups of patients with an expected high or low risk of subsequent wound infection for the study of prophylactic measures.

In the present study, examination was made of swabs taken during the operation from two different sites of the wound, and the bacteria isolated from the subcutis were correlated with bacteria isolated from infected wounds.

Materials and Methods

The investigation comprised 1200 surgical wounds from the Municipal Hospitals in Copenhagen (845 wounds) and Aarhus (355 wounds). Detailed information concerning the patients and the wounds has been published previously.[5,6]

During the operation, a swab was taken from opened hollow viscera for bacteriological examination. In the cases in which no viscus was opened, either no swabbing was made, or else a swab was taken from the operational field. These specimens are called "swab F."

At the termination of operation, another swab was taken from the subcutis just prior to final closure of the wound ("swab G").

All wounds were observed for signs of wound infection during the postoperative period. Where wound infection was suspected, swabs were taken from the wound ("swab L") and an attempt was made to classify the infection according to the following clinical criteria:—

Non-purulent Wound Infections:

(a) Erythema, marginal wound infection and/or serous secretion.

Purulent Wound Infections:

(b) Superfascial, purulent infections or abscesses.
(c) Subfascial or visceral purulent infections.
(d) Other kinds of purulent infections apart from (e) and (f).

Miscellaneous:

(e) Wound ruptures without clinical signs of infection.
(f) Purulent infections in perineal wounds following amputation of the rectum.

Non-purulent infections were omitted from the study, and thus the term "postoperative infection" covers subgroups (b), (c), (d), (e), and (f). Bacteriological examination was made of 615 swabs from the organ or the field and 973 swabs from the subcutis. A total of 233 purulent infections were found and from these 146 swabs were examined bacteriologically.

Dry, sterile cotton swabs were used for swabbing. The bacteriological examination was performed within a few hours and the bacteria were identified in the usual way.[3] The degree of contamination was estimated by standardized inoculation on solid media. Growth of 1–20 colonies was termed "moderate."

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TABLE 1. *Frequency of Postoperative Wound Infection According to Type of Operation (1200 Operations)*

		Wound Infection	
		No.	%
Colon operations	(135)	52	38.5
Appendectomy (perforated)	(22)	13	59.0
Urinary tract operations	(16)	7	44.0
Gastric operations	(172)	41	23.9
Biliary tract operations	(159)	35	22.0
Intestinal operations	(12)	3	25.0
Explorative laparotomy	(51)	9	18.0
Osteosynthesis	(235)	30	12.7
Appendectomy (no perforation)	(97)	4	4.0
Hernial operations	(62)	2	3.0
Varicose vein operations	(13)	5	39.0
Skin transplantation	(14)	1	7.0
Gynaecological operations	(13)	2	15.0
Removal of osteosynthesis	(75)	2	3.0
Various other operations	(124)	27	21.8
Total	(1200)	233	19.4

"Colon operations" include resection and colostomy.
"Gastric operations" include acute operations for perforated gastric and duodenal ulcers.
Figures in parentheses denote total number of operations performed.

Results

The types of operation and the frequency of wound infection are summarized in Table 1.

Specimens from the Organ and the Field (Table 2).

Escherichia coli were isolated from 143 F swabs, 168 gave growth of other bacteria, and 304 appeared to be sterile. Heavy growth of *E. coli* was followed by wound infection with the same species in 33.9 per cent of the cases, as compared with 2.3 per cent when the swab was sterile. Wound infection with other bacteria was rare in the cases in which there was heavy growth of *E. coli* in the organ or field. When other bacteria grew from the peroperative swab, infections occurred in 26.8 per cent but were rarely caused by *E. coli* (3.6%).

TABLE 2. *Correlation between Bacterial Contamination of the Wound during Operation (Swab F) and Postoperative Wound Infection*

Swab F: swab taken from organ during operation		Post-operative infection			
		E. coli		Other bacteria	
		No.	%	No.	%
Moderate growth of *E. coli*	(28)	5	18.0	5	18.0
Heavy growth of *E. coli*	(115)	39	33.9	3	2.6
Other bacteria	(168)	6	3.6	45	26.8
No growth	(304)	7	2.3	42	13.8
Not examined	(585)	15	2.6	66	11.3
Total	(1200)	72	6.0	161	13.4

Figures in parentheses denote total number of operations performed.

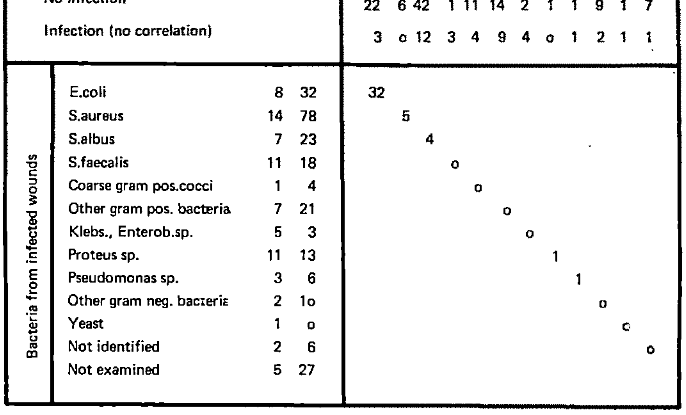
TABLE 3. *Correlation between Bacterial Contamination of the Wound during Operation (Swab G) and Postoperative Wound Infection*

Swab G: swab taken from subcutis during operation		Post-operative Infection				
		E. coli			Other bacteria	
		No.		%	No.	%
Moderate growth of *E. coli*	(27)	13		48.0	2	7.0
Heavy growth of *E. coli*	(30)	19		63.0	0	0
Other bacteria	(110)	8	33*	7.3	26	23.6
No growth	(806)	25		3.1	106	13.2
Not examined	(227)	7		3.1	27	11.9
Total	(1200)	72		6.0	161	13.4

* See explanation in text.
Figures in parentheses denote total number of operations performed.

Specimens from the Subcutis (Table 3).

E. coli were found in 57 samples from the subcutis, there was growth of other bacteria in 110 wounds, and 806 swabs were sterile. Moderate or heavy growth of *E. coli* was followed by sepsis with the same species in 48 per cent and 63 per cent of the cases, respectively, and infection with other bacteria occurred in two patients only. In patients with a sterile subcutis swab, infection with *E. coli* was registered in 3.1 per cent of the cases, and with other bacteria in 13.2 per cent. When bacteria



		No growth in subcutis or not examined	Growth in subcutis (no correlation)	Bacteria from subcutis: E.coli	S.aureus	S.albus	S.faecalis	Coarse gram pos.cocci	Other gram pos. bacteria	Klebs., Enterob.sp.	Proteus sp.	Pseudomonas sp.	Other gram neg. bacteria	Yeast	Not identified
No infection				22	6	42	1	11	14	2	1	1	9	1	7
Infection (no correlation)				3	0	12	3	4	9	4	0	1	2	1	1
Bacteria from infected wounds	E.coli	8	32	32											
	S.aureus	14	78		5										
	S.albus	7	23			4									
	S.faecalis	11	18				0								
	Coarse gram pos.cocci	1	4					0							
	Other gram pos. bacteria	7	21						0						
	Klebs., Enterob.sp.	5	3							0					
	Proteus sp.	11	13								1				
	Pseudomonas sp.	3	6									1			
	Other gram neg. bacteria	2	10										0		
	Yeast	1	0											0	
	Not identified	2	6												0
	Not examined	5	27												

FIG. 1. Two hundred bacterial strains found in 167 swabs from subcutis correlated with 329 strains isolated from 233 wound infections (swab L).

other than *E. coli* were isolated from the subcutis, infection followed in 23.6 per cent of the cases.

Wound infection with *E. coli* occurred in 33 patients where the subcutis was either sterile or contaminated with other bacteria. In 13 of these, the infecting germ was demonstrated in the organ swab, thus indicating faulty subcutis swabbing in some instances.

Correlation between Bacterial Species Found during Operation and in the Infected Wound.

It will be seen from Tables 2 and 3 that positive correlation was found between contamination during the operation and postoperative wound infection. At a bacterial species level, the correlation was significant as regards *E. coli,* especially when present in the subcutis, in which even the degree of contamination was reflected. Concerning the other bacteria, the apparent correlation could not be found at the species level (Fig. 1).

Thus, the subcutis swab revealed a small group of patients with a high frequency of postoperative infection with *E. coli,* and here the swab from the subcutis appeared to be superior to the swab from the organ or field. At a species level, the bacteriological examination of swabs taken during the operation was of no use in predicting types of infection other than those caused by *E. coli.*

Discussion

Contamination of the surgical wound seems to take place during the operation in a varying, but presumably considerable, number of cases.[2,4,7] Bacteriological examination of the wound during the operation reflects a fraction of the true contamination rate, dependent on the sampling technic and the operation in question.

The contaminaants could be classified into two major groups, *viz.* the intestinal bacteria represented here by *E. coli,* and a large variety of other bacteria including *Staphylococcus aureus.* In a previous study,[9] infecting bacteria of the coli group were found to originate mainly from the patients' own intestinal flora, and contamination of the subcutis with these microorganisms was associated with subsequent wound infection in more than half the cases. Thus, the major part of such infections are presumably caused by autoinfection during the operation.

The origin of the wide variety of other microorganisms found in the subcutis is not known. Some may be commensals carried on the skin prior to operation, and some were probably deposited in the wound from different external sources during the course of operation. In evaluating the ability of these contaminants to cause wound infection, it is of interest that there was only poor correlation between bacteria in the subcutis and in the infected wounds at a species level. Apart from a few obvious or occasional instances, bacteria (other than *E. coli*) isolated from the subcutis were not recovered from the infected wounds, and many wounds contaminated during the operation did not become infected later. Supported by the fact that coagulase-positive staphylococci were rarely found in the subcutis, though they caused numerous infections, these observations did not indicate a causal relationship between contaminants and wound infection. It might therefore be assumed that many of these infections were not contracted in the operating theatre. This conception is in agreement with the recent findings of other workers.[1,8]

In the present study, the swab from the subcutis was found to be superior to that from the organ or field for selecting a small group of patients with a high incidence of *E. coli* wound infection. Since this information can be available 1 or 2 days after operation and several days before clinical signs of wound infection will appear, the swab may be of use in controlled clinical prevention studies.

Summary

Bacteriological swabs from 1200 surgical wounds were collected from different sites of the open wound during the couse of operation.

Swabs from opened viscera or from the bottom of the operational field gave growth of *Escherichia coli* in 143 cases; 44 of these wounds were infected with the same microorganism postoperatively.

Swabs taken from the subcutis prior to final closure showed a higher degree of correlation with subsequent wound infection (57/32). Where the swabs taken during the operation appeared to be sterile, wound infection with *E. coli* was rare.

Thus, with the technic used, close connection was revealed between contamination of the wound edges with *E. coli* and wound infection. However, no correlation was found with other bacterial species, including coagulase-positive staphylococci.

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Mechanisms of Antibacterial Effect of Biologic Dressings

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SKIN COVERAGE of a contaminated wound results in its bacterial sterilization. This clinical observation was experimentally confirmed in 1958 by Eade[8] using partial thickness autografts, and both viable and nonviable homografts. Subsequently, homograft and heterograft skin used as temporary biologic dressings (BD) have confirmed both experimentally and clinically such a sterilizing activity on underlying contaminated granulating wound beds.[2,4,14–17]

This is a study of mechanisms by which partial thickness skin wound dressings effect antibacterial activity.

Experimental Methods

The Wound. Albino Sprague-Dawley rats weighing 180–200 Gm. were anesthetized with 1.0 mg./25 Gm. BWT intraperitoneal Sodium Pentothal and a 3 × 4 cm. ellipse of full thickness skin excised from the mid portion of the back. The underlying fascial bed was seeded with 1.0 ml. of a 1 day culture of *Staphylococcus aureus*. These wounds demonstrated classic signs of infection by 72 hours and by 5 days 30–50% of animals died of infection. Mortality after 5 days was negligible.

Surface Bacterial Counts 0.01 ml. of fluid from the surface of the wound was obtained with a calibrated inoculating loop and the contents plated in duplicate on blood agar followed by incubation for 48 hours at 37°C. Colonies were counted without magnification; more than 100 colonies per plate could not be counted with accuracy.

Tissue Bacterial Counts. A small wedge of tissue (2 × 3 mm. in diam.) was excised from the central portion of the granulation tissue using sterile forceps and scissors. Destruction of surface bacteria was achieved by dipping this specimen for one second into absolute ethanol followed immediately by igniting and allowing the flame to burn out spontaneously (±3 seconds). The flamed specimen was weighed and placed in sterile 5.0 ml. physiologic saline. Under sterile conditions, the suspended specimen was placed in a petri dish with sand and ground with a glass rod. Duplicate 0.01 ml. specimens of the homogenate were plated on blood agar with the calibrated platinum loop. Forty-eight hours after incubation at 37°C. colony counts were performed.

Procurement of Biologic Dressings

1) Split thickness autograft rat skin, 0.015 inch in thickness, was harvested with a Padgett Drum Dermatome. Skin preparation was solely by clipping the hair and shaving the stubble. The skin was stored at 3–5°C. in Ringer's solution.

2) Split thickness Porcine Skin, 0.020 inch thickness, was harvested from young anesthetized pigs with a Brown Dermatome. Prior to taking the graft the hide was scrubbed with soap then shaved. Final skin cleansing was with saline rinse, a Zephiran Chloride 1/750 soak and another saline rinse. These precautions were taken to avoid residual antiseptic on the skin graft which might have antibacterial activity distinct from the skin as a biologic dressing. The sterile porcine skin was stored at 3–5°C. in Ringer's solution until ready for use.

3) Frozen irradiated split thickness pig skin [*] which had been frozen at −50°C. and exposed to 2.5 million rad was thawed and stored at 3–5°C. in Ringer's solution awaiting use as a biologic dressing.

4) Split thickness porcine skin was also obtained from the Burn Treatment Skin Bank, Inc. and similarly stored at 3–5°C. until used. This unirradiated commercially

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[*] Burn Treatment Skin Bank, Inc., Phoenix, Arizona.

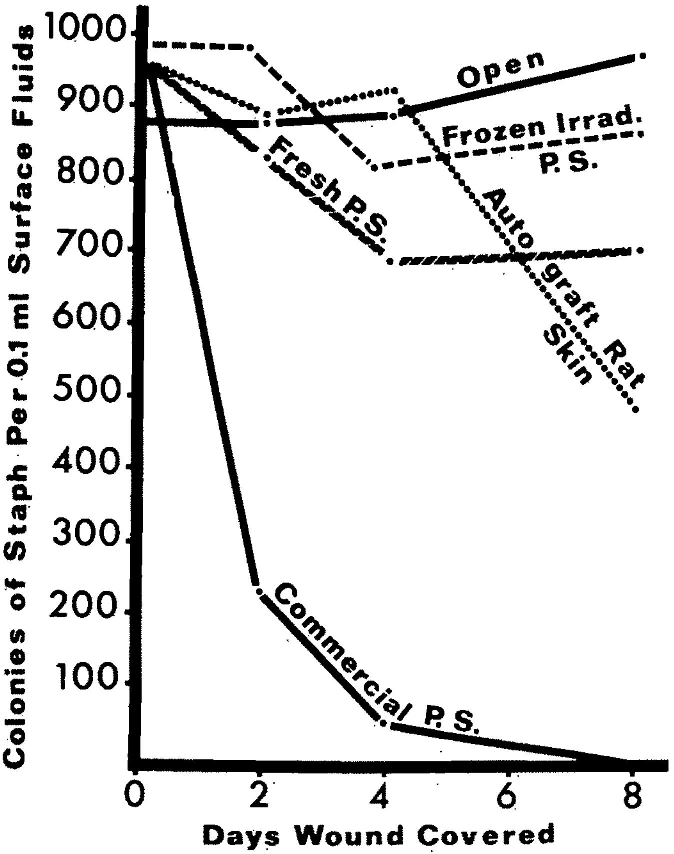

FIG. 1. Graph Illustrating Wound Surface Bacterial Counts after Coverage with Various Types of Partial Thickness Skin Dressings.

available porcine skin had been cleansed with and contained traces of Betadine and Neomycin solutions.

Application of Biologic Dressings

The infected granulating wound bed was wiped dry with a sterile gauze sponge 7 days following seeding with staphylococcus and the appropriate type of skin was used as a temporary biologic dressing. Seven to 10 Michael Clips held the skin dressing to the edge of the wound. The split thickness autograft skin was left undisturbed for 8 days. All other biologic dressings were replaced every 48 hours.

Surface vH Determination. Subcutaneous pH was determined by passing an Instrument Laboratory glass electrode connected to a Beckman Expanded Scale pH Meter through a small incision made in the skin of the back of the anesthetized animal. The pH of uncovered infected granulation tissue was determined by placing the probe on the surface of the granulations. pH of granulations beneath a skin dressing was measured by lifting an edge of the skin and immediately making contact with the underlying granulation bed with the probe.

All pH determinations were made in triplicate in different areas of the wound.

Determination of Tissue Po$_2$. An International Biophysics Corporation Differential Oxygen Analyzer [*] was used to determine the tissue Po$_2$. The instrument was calibrated prior to each experiment using water open to room air as a 120 mm. Hg Po$_2$ reference. The small probe was passed through a #15 gauge needle into normal subcutaneous tissue or from normal skin and subcutaneous tissue adjacent to a BD covered wound into the granulation tissue under study. Each determination was made in duplicate using a 5-minute equilibration time.

Tissue and rectal temperature of anesthetized rats was recorded with a Yellow Springs Instrument Co. Tele-Thermometer. Temperatures were recorded by inserting the probe into the tissue through a long subcutaneous tract. Immediately thereafter rectal temperature was recorded and the difference between the rectal and tissue temperatures were recorded.

Histology. Biopsies of granulating beds were taken at various times. The tissue was placed in 10% buffered formalin, sectioned at 4 microns and stained with hematoxylin and eosin.

In Vivo Effect of BD on Bacterial Counts

Seven days after inoculation of the wound bed with *Staphylococcus aureus* the animals were randomly divided into 4 groups of 10–20 rats each.

Group I. No Wound Coverage.

Group II. Split Thickness Autograft Coverage.

Group III. Fresh Split Thickness Porcine Skin Coverage.

Group IV. Commercial Porcine Skin Coverage.

Surface bacterial colony counts were performed prior to coverage and every 2 days when the BD was changed. Tissue bacterial colony counts were performed prior to coverage and on the fourth and eighth post-coverage days. These experiments were ended on the eighth post-coverage day. Because autogenous skin dressings were not removed every 48 hours surface cultures on Day 2 and 4 were performed by lifting a small corner of the dressing for sampling. Animals biopsied for tissue bacterial quantitation were not used for surface studies because of the irregularity of the granulation bed produced by the biopsy.

Group I. Uncovered infected wounds (13 animals)—As shown in Figures 1, 2 and Tables 1, 2, surface cultures of the uncovered wounds remained at 1,000 colonies/0.1 ml. in most animals throughout the 8-day study period. Bacterial counts of the tissues similarly were essentially unchanged being 420,000 organisms/0.1 Gm. tissue on the first day and 484,000 on the 8th day. There clearly was no significant spontaneous antibacterial effect in the animals except for one who for unknown reasons had

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[*] Kindly supplied by Mr. Bockhaus, International Biophysics Corp., Irvine, Calif.

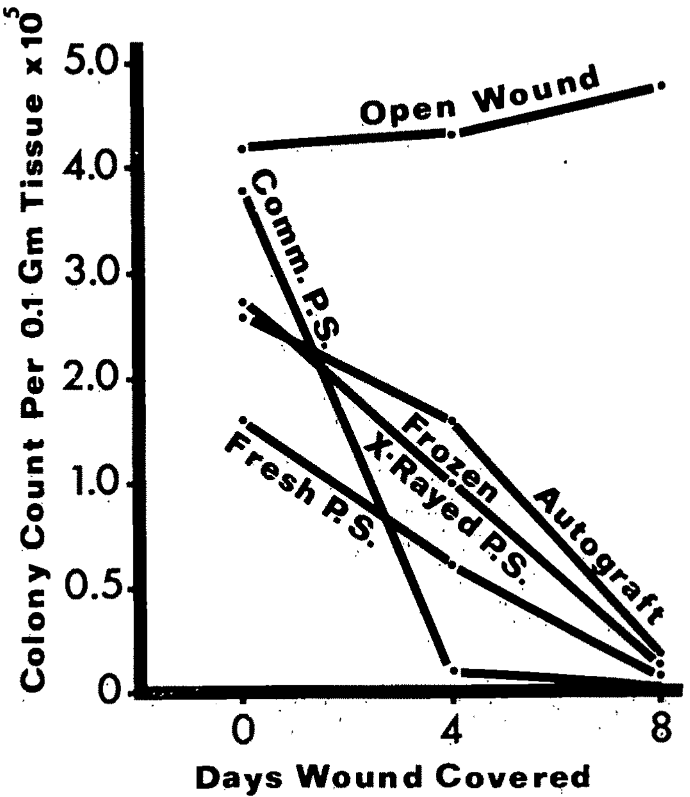

FIG. 2. Graph Illustrating Wound Granulation Tissue Bacterial Counts after Coverage with Various Types of Partial Thickness Skin Dressings.

TABLE 1. *Wound Surface Bacterial Counts after Coverage with Various Types of Partial Thickness Skin Dressings*

	(Bacterial Colonies/0.1 ml Surface Fluid)				
Day	Open Wound	Autograft Skin	Fresh Porcine Skin	Commercial Porcine Skin	Frozen Irradiated Skin
0	888	975 ± 70	925 ± 75	1000	1000
2	888	900	845	240	1000
4	910	940	700	54	832
8	1000	500 ± 465 $p < 0.005$*	725 ± 290 $p > 0.20$*	0	890

* Compared to Day 0

a sterile open wound at the end of the 8-day study. The remainder continued to have frankly infected wounds.

Group II. Autografts (9 animals)—As documented in Figures 1, 2, and Tables 1, 2, graft coverage significantly diminished bacterial counts.

Surface counts were sterile in two animals by the 8th day and were significantly below 1,000 colonies/0.1 ml. in four other animals. Reduction in surface bacteria was insignificant until after Day 4 on the wounds covered with autograft skin.

Uniformly, bacterial reduction was more prompt and more complete within the granulations than on the wound surface. Seven of nine animals had sterile granulations on Day 8; in the other two animals bacteria were less than 25,000 colonies/0.1 ml. at the end of the study.

Group III. Partial Thickness Porcine Skin (16 animals) —Surface bacterial counts at each 48 hour BD change demonstrated insignificant change during the 8 day observation period as illustrated in Figure 1 and Table 1.

Bacterial counts in the granulation tissue in contrast showed significant diminution. Ten of 16 animals had sterile granulation tissue by the 8th day and the other six all showed significant reduction in the number of bacteria per 0.1 Gm. tissue by the 8th day. (Figures 2 and Table 2)

Group IV. Commercial Split Thickness Pig Skin—As shown in Figures 1, 2 and Tables 1, 2, wounds redressed every 2 days with a commercially available Pig Skin sterilized most quickly.

Surface fluid bacteria counts were markedly reduced by Day 4 and by Day 8, at the end of the study, all surfaces were sterile.

Cultures of the granulating beds were sterile in every one of the 11 animals by Day 8.

In Vitro Antibacterial Activity of BD

To determine whether some property of the BD itself might be producing the antibacterial effect, specimens of

TABLE 2. *Wound Granulation Tissue Bacterial Counts after Coverage with Various Types of Partial Thickness Skin Dressings*

	Bacterial Colonies/0.1gm Tissue					Sterile Beds		
	Days Covered							
Coverage	0	4	8	P* Value	% Change Mean Bacterial Counts	#	# Test Animals	%
Open Wound	420,000	430,000	484,000	—	+20	1	13	8
Autograft Skin	255,000	173,000	6,000	<0.025	−97	7	9	78
Fresh Porcine Skin	174,000	57,000	3,700	<0.005	−98	10	16	62
Commercial Porcine Skin	384,000	570	0	—	−100	11	11	100
Frozen X-Rayed Porcine Skin	270,000	100,000	4,800	<0.05	−98	5	10	50

* Day 8 compared to Day 0

the various dressings were placed on blood agar plates seeded with the same strain of *Staphylococcus aureus* used to contaminate the wound. Bacterial inhibition was judged by a 3–6 mm. halo of inhibited bacterial growth and by subculturing the surface of the agar beneath the skin at 48 hours.

The following substances were tested for antibacterial activity *in vitro.*

Group I. Full Thickness Rat Skin (10 expts)
Group II. Split Thickness Rat Skin (10 expts)
Group III. Fresh Split Thickness Pig Skin (10 expts)
Group IV. Commercial Pig Skin (10 expts)
Group V. Gauze backing on commercial Pig Skin (10 expts)

The only substances that in any way interfered with bacterial growth were commercially available Pig Skin and the gauze backing used in its packaging. Partial and full thickness antogenous skin and fresh partial thickness porcine skin did not inhibit growth of staphylococcus.

Since the only difference between commercially available split thickness Pig Skin (Group IV) and Fresh Pig Skin (Group III) was the antibiotic and iodophore treatment, it was concluded that *in vitro* bacterial inhibition by commercial Pig Skin was due to retention of these substances—not to an inherent quality of the skin itself.

Properties of BD That Could Effect Antibacterial Activity

The following possible etiologic factors in antibacterial activity were evaluated:

1) Vascularization of the BD.
2) Viability of the BD.
3) Adherence of BD to granulating bed.
4) Exclusion of the wound granulations from the external environment without adherence of the BD to the granulations.
5) Wound environment beneath the skin dressing.

Vascularization of the skin dressing as the prerequisite factor was eliminated by changing the wound dressing every 2 days. Vascularization of the autograft skin did appear to correlate with a decrease in surface or interface infection. The degree of infection remained constant in the other groups but steadily decreased after the fourth day in the autograft group.

Skin viability as an important factor was eliminated by the antibacterial effectiveness in 10 animals of frozen irradiated pig skin as shown in Figures 1, 2 and Tables 1, 2.

Surface bacterial counts remained unchanged. Counts in the granulation tissue were however significantly decreased. Five animals had sterile granulations and in the other five, bacterial counts were significantly diminished (mean of 270,000 colonies/0.1 Gm. to mean of 4,800 col/0.1 Gm.) by the 8th day.

Adherence of Biologic Dressing. Immediate adherence of a skin graft to a raw wound bed is a common observation but the nature of the bond is little understood. Correlation of adherence with antibacterial effect was first tested by turning 12 xenografts upside down with the epidermal surface in apposition to the wound bed. As anticipated, the inverted skin did not adhere and the granulating bed remained frankly infected. Both surface bacterial counts (mean colony counts > 1,000 col/0.1 cc. fluid on Day 0 and on Day 8) and mean counts in the granulations (78,000 colonies/0.1 Gm. tissue on Day 0 and 130,000 colonies/0.1 Gm. tissue on Day 8) were unchanged or increased in 8 days in all 12 animals tested. Inverted skin dressings that did not adhere to the wound were of no antibacterial benefit.

Isolation of Granulations From Environment. Sealing of the infected wound from the external environment without adherence of the BD to the granulations was achieved in 12 experiments by insertion of a sheet of plastic parafilm* beneath frozen irradiated porcine skin held in place with clips. The interposed plastic prevented skin adherence to the granulations but the edges of the skin dressings were sealed to the wound skin edge. The entire plastic and skin coverage was changed every 2 days. The wound invariably remained infected without decrease in surface or granulation bacterial counts.

Wound Environment Beneath BD. Tissue pH, Po_2, temperature and histologic appearance of the granulating bed beneath BD coverage were determined as they altered the environment for bacterial growth, and/or host defense mechanisms.

In 20 rats normal subcutaneous tissue pH was 7.75 ± 0.02. Uncovered infected granulation tissue surface pH was 7.66 ± 0.09. Twenty-four hours after coverage with frozen irradiated pig skin granulation tissue surface pH was 7.59 ± 0.05, a difference small but highly significant ($p < 0.0005$). BD decreased alkalinity of the granulations. No causative relation is necessarily implied by this correlation which could be an effect not a cause of decreased bacterial contamination.

In 20 rats normal subcutaneous Po_2 was 27 ± 4.9 mm. Hg. Uncovered contaminated granulations had a Po_2 of 34 ± 5.5 mm. Hg. Twenty-four hours following BD coverage with frozen irradiated pig skin Po_2 of the wound bed was 36 ± 6.8 mm. Hg. These differences between open and covered granulations were not significant.

Mean temperature in 20 rats of the normal subcutaneous tissue was 2.1 ± 0.6°C. lower than rectal temperature (Table 3). Temperature of uncovered granulation tissue was 3.8 ± 0.6°C. lower than rectal temperature. Temperature beneath the skin dressing 24 hours after coverage was 1.7 ± 0.6°C. lower than rectal temperature.

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* Marathon Products, Nunan, Wisconsin.

As listed in Table 3 these small differences were statistically significant.

Histologic evaluation of uncovered infected granulation tissue showed the expected dense infiltration of polymorphonuclear leukocytes in the granulation tissue and a thick band of dead or dying leukocytes on the surface. The infected granulation bed covered for 48 hours with a BD showed virtually no leukocytes at the interface between the granulation tissue and the biologic dressing.

Discussion

These experimental data confirm and quantitate the common clinical observation that an infected wound covered with an autograft or with skin changed every 2 days and thus used as a biologic dressing is followed by sterilization of the wound. Of most timely clinical importance is the use of homograft skin,[1,5,9,12,13,18,19,21] and porcine heterograft skin[2,4,10,15,16,17,19] for treatment of burns and other infected wounds. The problem in its broader sense involves the effect of a biologic dressing over an infected wound.[6,15]

Confirming both clinical and other experimental data,[22,16] skin viability is not essential for the antibacterial effect of a biologic dressing. Frozen irradiated skin was equally effective as was fresh skin.

Skin dressings sterilize an infected wound not by any inherent property of the skin but apparently by augmenting the host immunologic defense. The slight acidity[3] and increase in tissue temperature beneath skin coverage[10] improve phagocytosis but may not significantly alter bacterial growth. Of prime importance probably is the removal and subsequent prevention of accumulation of leukocytes on the surface of infected granulations by the adherent biologic dressing. Dying leukocytes or leukocytes active in phagocytosis may liberate a substance that reduces phagocytosis.[20] Prevention of accumulation of this hypothetical antiphagocytic factory by prevention of exudation of leukocytes may allow the host animal to sterilize his granulating bed.

BD coverage is slow in asserting its antibacterial effect. In this experimental model sterilization of the granulation tissue significantly preceded decrease in surface bacteria, a finding in conflict with data reported by Eade.[8] The rapid disappearance of surface bacteria reported by Eade may have been due to persistent traces of hexachlorophene and other bactericidal substances used in preparing the skin dressings. In these studies, using commercially available pig skin contaminated with antibiotics, we obtained similar surface sterilization but failed to achieve surface sterilization when Betadine and Neomycin preparation was omitted.

Autograft skin coverage achieved diminution of surface counts after the 4th day when the graft became vascularized. In the absence of skin dressing vascularization (heterografts) the surface bacteria persisted even though underlying granulations became sterile.

TABLE 3. *Difference in Tissue and Rectal Temperature after Coverage of Infected Granulating Wounds with Partial Thickness Skin Dressings*

	Number Animals	Difference Rectal & Tissue Temp.	P Value
Normal Subcutaneous Tissue	20	+2.1 ± 0.65	—
Open Infected Granulation	20	+3.8 ± 0.67	Compared to Normal <0.005
Covered with Partial Thickness Skin	20	+1.7 ± 0.6	Compared to Uncovered Granulation <0.005

In these studies the skin coverage was changed every 48 hours. Removal and replacement of the adherent dressing could mechanically aid wound debridement as do frequent changes of a wet dressing.

Adherence of the BD to the granulating bed was common to each BD that was found to result in tissue sterilization. Dressings that did not tightly bond to wound granulations did not effect a decrease in tissue bacteria. Inverted skin with corium in contact with the wound bed is a case in point, it neither sticks nor sterilizes. Analysis of mechanisms that cause BD to adhere to wound granulations is therefore of both theoretic and practical importance. It has now been demonstrated that the adherence mechanism is related to a fibrin-elastin biologic bond.[21]

Summary

1) The effect on bacterial counts of various types of skin used as a dressing over infected wounds has been analyzed in 142 rat experiments.

2) Bacterial counts within the wound tissue decreased significantly by the 8th day with BD coverage. Bacterial counts fell by 98% and the wound was sterile in 50–78% of the experiments. Sterilization of granulation tissue precedes disappearance of bacteria on the wound surface.

3) Skin dressings caused a slight (2.1°C.) increase in wound temperature and a decrease of 0.007 units in alkalinity. Oxygen tension was not significantly altered. These changes in wound environment are unlikely to account for the antibacterial activity. Histologically, the BD prevents the accumulation of pus on the surface of the granulation tissue.

4) Exclusion of the wound from the environment with a non adherent BD, vascularization of the skin dressing, viability of the skin and inherent immunologic proper-

ties of the BD have all been eliminated as of casual importance

5) Adherence of the BD to the underlying contaminated wound bed was invariably associated with subsequent wound sterilization and is suspect of causal relationship. Skin that stuck sterilized.

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Sequential Hemodynamic Changes in Patients with Head Injury:

Evidence for an Early Hemodynamic Defect

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In man, cerebral injury with its attendant ischemia is frequently associated with increased cardiac output and arterial pressure.[1,5] This is consistent with experimental observations that these initial hemodynamic changes result from peripheral vasoconstriction and increased ventricular contractility.[2,4] However, recent clinical and experimental evidence indicates that cardiac output and peripheral resistance decrease if cerebral ischemia persists longer than a few minutes.[2,9] The resultant hypotension and decreased blood flow may have a significant influence on the degree of neurological recovery.[3]

The present studies were designed to delineate more precisely those cardiovascular changes associated with cerebral injury in man. Our objectives were to describe sequential hemodynamic patterns of surviving and nonsurviving patients. This was done in attempt to define those changes indicative of a poor prognosis and to suggest physiologic criteria which may be used to guide therapy. The assumptions are that if the early physiologic events associated with death can be characterized, they may serve as predictive indices and be useful for early warning.[12] Secondly, the characteristic physiologic patterns of survivors may be used as criteria for therapy.

Materials and Methods

Clinical Material

Sequential hemodynamic measurements were made in 17 normal subjects and 11 patients who had sustained cerebral contusion. Four of these patients survived and seven died from the effects of the head injury. Measurements were made remote from the time of specific therapeutic manipulations and during relatively stable periods when the patient did not exhibit anxiety, restlessness or agitation. These observations, in so far as possible, represent the natural history of cerebral ischemia in nonsurviving and surviving patients from the hemodynamic point of view. The clinical data are summarized in Table I.

Criteria for Separation of Data into Stages

Hemodynamic changes were separated into early, middle and late periods in each group of patients to describe their temporal sequence and to permit statistical correlations of the data at comparable stages.[13] The mean arterial pressure was chosen because, although arbitrary, it provides an objective criterion. A control period prior to onset of the etiologic agent or the post-recovery control period was defined as Stage A. Stage B was defined as the initial period of falling pressure immediately after the head injury. The lowest recorded arterial pressure (Stage *low*) separated this early period from the middle period (Stage C). The latter often was coincident with the onset of therapy and because of its length, it was divided into Stages C_1 and C_2 by the point in time when arterial pressure returned half way to normal. The late period (Stage D) was defined in survivors as the recovery period, when the patient had returned to a normal or nearly normal state from the

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TABLE 1. *Summary of Clinical Data*

Patient No. Sex, Age	Surface Area, Sq. Meters	Angiographic Diagnosis	Surgical Procedure	Associated Injury	Stage during Study Period	Results
1 M 44	2	intracerebral hematoma	partial temporal lobectomy for decompression	none	B low C_1C_2	died
2 M 59	2	epidural hematoma	temporal craniotomy	skull fracture	B low C_1C_2	died
3 M 24	2.10	acute subdural hematoma cerebral contusion	temporal craniotomy partial temporal lobectomy for decompression	fracture femur fracfracture radius	B low C_1C_2	died
4 M 40	1.90	cerebral contusion and edema	none	none	B D	survived
5 M 58	1.50	acute subdural hematoma and cerebral contusion	temporal craniotomy partial temporal lobectomy for decompression	none	E	died
6 F 53	2	acute subdural hematoma temporal lobe contusion	temporal craniotomy	none	B low C_1 E	died
7 M 50	2	acute subdural hematoma temporal lobe contusion	temporal craniotomy partial temporal lobectomy for decompression	none	C_2	died
8 M 58	1.98	epidural hematoma	temporal craniotomy	skull fracture	B low C_1C_2	survived
9 M 50	2.00	subdural hematoma	burr holes evacuation of hematoma	none	B low C_1 D	survived
10 M 59	2.00	epidural hematoma	temporal craniotomy	none	C_1C_2 E	died
11 M 25	2.10	epidural hematoma	temporal craniotomy	skull fracture	B C_1C_2	survived

point of view of arterial pressures. Stage E was defined as the preterminal period in the course of patients who subsequently died.

Technic of Hemodynamic Measurements

Central venous catheters were placed in the superior vena cava via percutaneous puncture of the subclavian vein. A six inch #17 plastic needle was inserted into one of the femoral arteries by percutaneous puncture. The intravascular pressures were measured directly with pressure transducers and recorded on a multiple channel direct writing recorder; heart rate was measured directly from these recordings. Cardiac output was measured by the indicator dilution method of Stewart-Hamilton[6] with indocyanine green as the indicator. Arterial dye concentrations of indocyanine green were measured continuously before and after the dye injection with a Gilford photodensitometer, a constant withdrawal syringe and recorder. Sterilized teflon tubing was used in all connections so that the patient's blood could be replaced after each determination.

Cardiac output was calculated from the area under the primary washout curve by a digital computer and a program which used an algorythm based on ratios of the log of digital values taken every 0.1 second in order to differentiate the dye recirculation from the primary washout curve. In over half of the curves of the present series this calculation was checked by manually replotting the curves on semilog paper. The mean transit time, peripheral resistance, central blood volume, stroke, left ventricular stroke work, and left cardiac work were calculated according to standard formulae by a digital computer programmed for this purpose; all measurements involving flow were indexed by dividing by the patient's surface area.

Results

Hemodynamic Measurements of the Entire Series

The hemodynamic data of the series as a whole are summarized in Table 2. The mean arterial pressure fell progressively during the B and *low* stages, then rose in

TABLE 2. *Summary of Hemodynamic Data of the Entire Series*

	Normal Values	B	Low	C_1	C_2	D	E
Cardiac index (1/min/M^2)	3.2 ± .05*	3.0 ± 0.6	2.6 ± .5	3.5 ± .6	4.2 ± .6	4.4 ± .04	2.9 ± 1.3
Heart rate (beats/min)	71 ± 1.6	118 ± 8.4	122 ± 8.9	109 ± 7.7	98 ± 7.1	101 ± 14	94 ± 14
Mean arterial pressure (mm. Hg)	92 ± 1.1	88 ± 11	61 ± 8.8	81 ± 8.6	91 ± 9.5	83 ± 8.3	52 ± 2.8
Central venous pressure (cm saline)	6. ± .4	3.2 ± 3.3	0.6 ± 3.3	2.1 ± 4.1	4.2 ± 4.0	8.2 ± .1	10.8 ± 6.5
Central blood volume (ml./M^2)	830 ± 25	844 ± 117	801 ± 81	901 ± 123	1025 ± 111	968 ± 32	1288 ± 581
Systemic vascular resistance (dyne·sec/cm^5/M^2)	2178 ± 57	2803 ± 701	2051 ± 343	2006 ± 234	1743 ± 246	1433 ± 177	1846 ± 683
Stroke index (ml./M^2)	46 ± 1.1	26.1 ± 5.2	20.7 ± 3.1	34.3 ± 5	45 ± 7.7	44.5 ± 5.7	37 ± 21

* S.E. of the mean

the C_1, C_2 and D stages and fell to very low values in the preterminal (E) stage.

The mean cardiac index for this entire series was slightly less than control values in the initial period of declining arterial pressure (stage B). At the time of maximal hypotension, the cardiac index decreased further. In the C_1, C_2 and D the cardiac index increased above the values of the normal control subjects.

The average heart rate increased above control values in stages B and *low;* it progressively declined during stage C_1 and C_2 when mean arterial pressure and cardiac index were increasing. No significant differences in heart rate were noted between the D and E stages.

Central venous pressure remained relatively low until the preterminal stage, where it rose to an average of 11 cm. of saline (Table 2).

The changes in stroke volume were similar to those of the cardiac output during all periods of study. The stroke volume decreased in the *low* stage and increased to normal values in the C and D stages. Since the heart rate declined slightly from the earlier periods of observation, the increased cardiac index was a function of increased stroke volume. The central blood volume was normal or only slightly decreased during the B and *low* stages; subsequently these increased above the control values in stages C, D and E.

The patterns of changes in left ventricular stroke work and minute work were similar. In the *low* stage, these values decreased below the earlier B stage and control values. By contrast, the middle and late periods (C and D stages) were characterized by increased stroke work and cardiac work to values above normal; the preterminal values were lower than normal (Table 2).

Comparison of Data From Survivors and Nonsurvivors

The data from the survivors and nonsurvivors were compared at all stages in order to characterize the entire sequence of events and to search for early changes which may have predictive value. Significant differences in the hemodynamic values of the two groups of patients began to appear in the B stage (Figs. 1 and 2). For example, the nonsurviving group had greater decreased in the mean cardiac index and greater increased in peripheral resistance in the B state, when both groups had

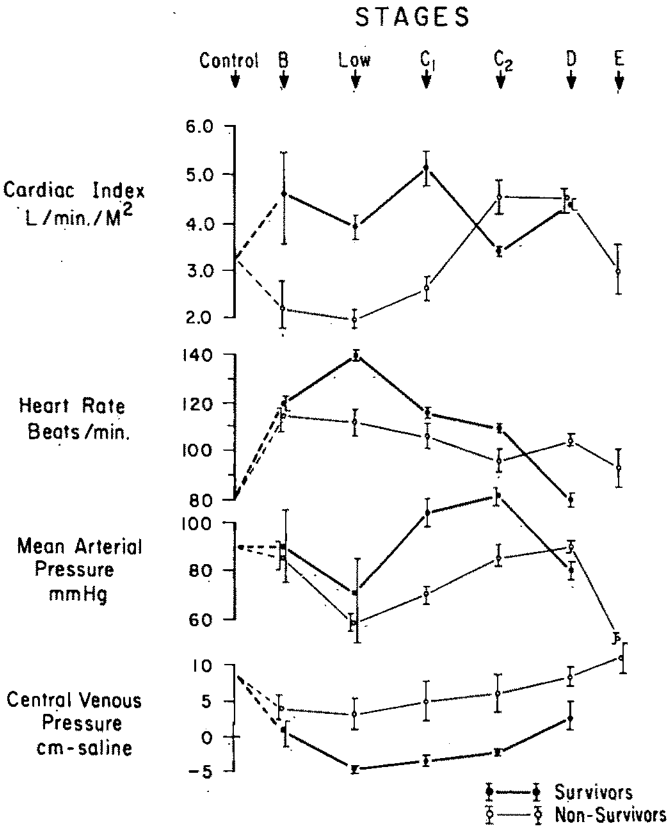

FIG. 1. Sequential patterns of the primary hemodynamic variables of survivors and nonsurvivors. Mean values are indicated by dots, and the standard errors by the vertical bars.

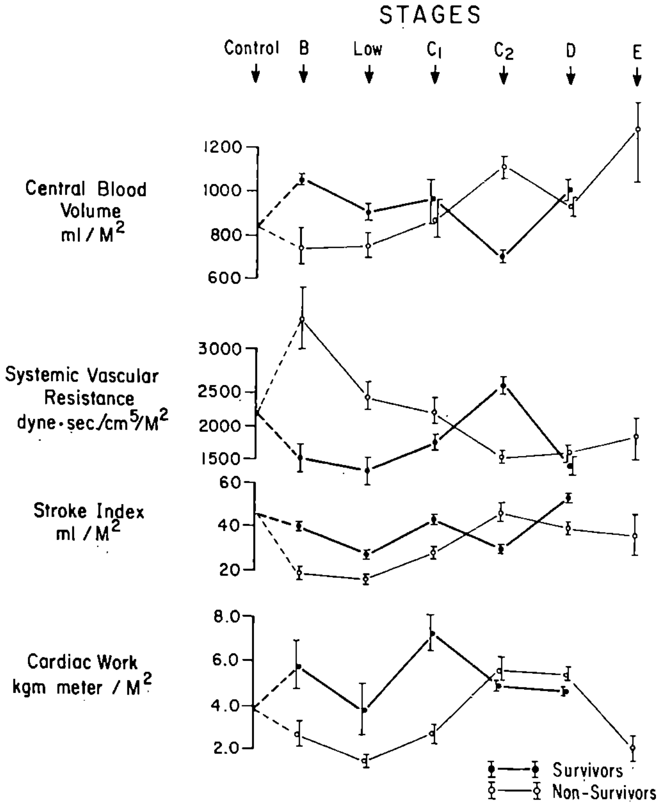

FIG. 2. Sequential patterns of the derived hemodynamic variables of survivors and nonsurvivors. Mean values are indicated by dots and the standard errors by the vertical bars.

roughly comparable arterial pressures and heart rates. Central blood volume, stroke volume, left ventricular stroke work and cardiac work of the nonsurvivors were also more depressed during the B stage.

During the low stage, the hemodynamic pattern of the nonsurviving patients was characterized by a low cardiac index and return toward normal values of peripheral resistance, but no significant increase in heart rate. When compared with the patients who survived, this group had significant differences in central blood volume, stroke volume, left ventricular stroke work and cardiac work, but these differences were not as great as those observed during the initial period of observation.

In general, the patterns of both groups tended to return to or above control values in the middle period (Stages C_1 and C_2) and the patterns tended to converge with less differences between the two groups. During the C_1 stage, the group of nonsurviving patients had slightly lower cardiac index, stroke index, stroke work and cardiac work than did the survivors. In the C_2 stage, both groups were roughly comparable in terms of cardiac index, stroke work, and cardiac work. The mean peripheral resistance in the nonsurvivors was lower than that of the survivors for the first time. Similarly, in Stage C_2 the mean central blood volume, which previously had been lower in the nonsurviving group increased over that of the survivors.

In the preterminal (E) period, the patients who subsequently died had relatively normal heart rates, hypotension, decreased cardiac output and reduced stroke volume. Systemic resistance and central blood volume during this period were slightly elevated when compared to the values observed in the late period (*i.e.* D stage) of surviving patients.

Discussion

The data from all of the patients with head injury show significantly altered hemodynamic variables that vary in the time course of the clinical syndrome. Comparison of the sequential changes in the surviving and nonsurviving patients revealed marked differences in the

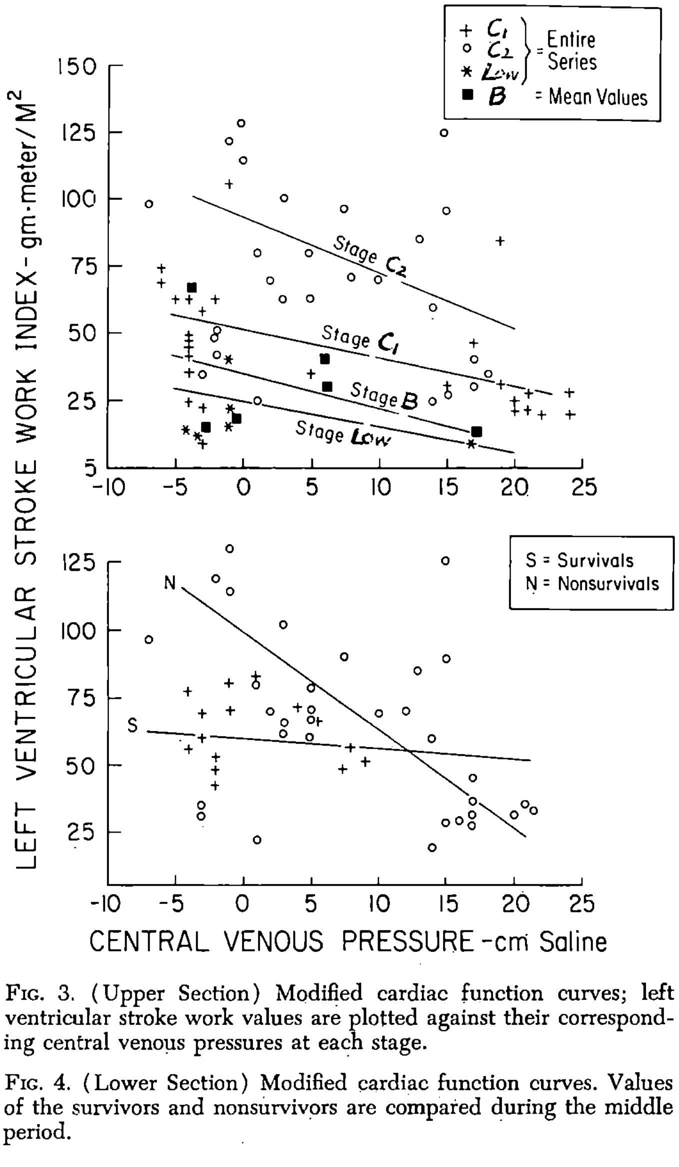

FIG. 3. (Upper Section) Modified cardiac function curves; left ventricular stroke work values are plotted against their corresponding central venous pressures at each stage.

FIG. 4. (Lower Section) Modified cardiac function curves. Values of the survivors and nonsurvivors are compared during the middle period.

early period (Stage B and *low*) that appear to have prognostic as well as therapeutic importance.

In the early period after injury, the mean hemodynamic values of the entire series of patients with head injury were relatively normal except for high peripheral resistance and tachycardia. There are at least three possible components of the initial compensatory hemodynamic response to cerebral ischemia: tachycardia, peripheral vasoconstriction and increased myocardial contractility.[2,4] These responses originate in or are mediated by, the vasomotor center.[11] The effect of these initial responses is to maintain or increase total blood flow and preferentially direct it toward organs of relatively low vascular resistance. The tachycardia and high peripheral resistance observed in the B stage may be interpreted as manifestations of this initial neural response to cranial trauma. Increased myocardial contractility is a very early and transient response to cerebral ischemia.[4] If contractility had increased in this group of patients, it most likely occurred immediately after injury and before our initial observations. A "modified cardiac function" curve constructed from the initial measurements of right atrial pressure and left ventricular stroke work in the B and *low* stages is characteristic of a myocardium with diminished contractility (Fig. 3).

Clinical and experimental observations previously reported from this laboratory indicate that sympathetic activity increased after mild or moderate degrees of cerebral ischemia of short duration, but decreased after severe degrees of prolonged cerebral ischemia; *i.e.*, mild transient cerebral ischemia acts as a stimulus to the central sympathetic centers, but severe, prolonged cerebral ischemia depresses them.[2] During the *low* stage, the heart rate and central venous pressures did not change significantly; but peripheral resistance, and left ventricular stroke work decreased. The fall in peripheral resistance may be interpreted as indicating decreased peripheral vasoconstriction. Myocardial contractility was severely depressed as evidence by the decreased left ventricular stroke work relative to the right atrial pressure (Fig. 3). This decreased in myocardial contractility and peripheral arteriolar tone probably results from depression of central sympathetic regulatory areas.

The restoration of cardiac index in the middle and late periods to values above those noted in the B early period is mainly a function of increased stroke volume. The upward shift of the ventricular function curve suggests that the increased stroke volume represents recovery of myocardial contractility, which had been depressed in the early period (Fig. 3). Increased stroke volume may also result from volume loading or redistribution of blood volume, but CVP and central blood volume in the middle and late period were not significantly increased in the series as a whole. The increased blood flow to values greater than normal in the recovery period may be needed to maintain oxygen delivery in the face of increased metabolic demands.[12]

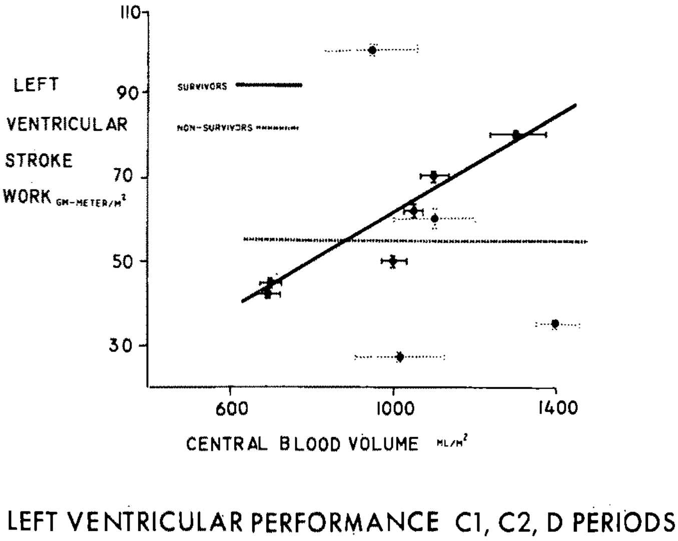

FIG. 5. Ventricular performance; left ventricular stroke work plotted against central blood volume. Data of survivors are compared with those of nonsurvivors.

It is of interest that surviving and nonsurviving patients exhibited markedly different hemodynamic patterns in the early stages when it is difficult to predict outcome by clinical criteria. During the B stage, nonsurviving patients maintained arterial pressures at the expense of reduced blood flow; this compensatory mechanism was transient as peripheral resistance values markedly decreased just before and during the *low* stage. Subsequently, stroke volume increased in both groups of patients, but the increase was greater in the survivors. The increased stroke volume in the nonsurvivors was associated with increased central blood volume in the C_2 stage.

The ventricular function curves suggest that the nonsurviving patients did not recover contractility to the same degree as did the survivors (Fig. 4). Consequently, the nonsurvivors required larger increments in central blood volume to generate equivalent stroke work (Fig. 5). It is postulated that after cerebral trauma, the heart of nonsurvivors behaves as if it were functionally denervated; that is, only a limited stroke volume increase is associated with the increased available blood represented by the central blood volume.

Finally, the patients with fatal head injury, were capable of restoring blood flow to normal values in a manner similar to that of the survivors during the C_2 stage. The increase in blood flow, while apparently appropriate in terms of the control values, may not have occurred soon enough, since the restoration of flow did not affect the final outcome.

The fact that the two groups of patients were similar at the end of the middle and late periods, lends even greater importance to the early findings of low cardiac index values in nonsurvivors. Presumably, the findings of low output in the early period immediately postinjury occurred before cerebral swelling was maximal. Cerebral oxygenation is precarious at this time because of changes in vessel walls, decreased blood flow, and microcirculatory alterations.[8,10] If cardiac output is depressed, then the fraction available for cerebral perfusion may be reduced even if there is some degree of preferential redistribution of blood flow away from peripheral tissues and toward the brain. Therefore, it would seem advisable to administer agents capable of increasing cardiac output and cerebral blood flow early in the course of head injury before systemic hypotension and reduced blood flow occur. The basic assumption of this therapeutic approach is that, if the hemodynamic pattern of nonsurvivors can be reversed, mortality may be improved.

Experimental studies support this view; animals who became hypotensive as a result of cerebral ischemia showed better neurologic recovery if systemic pressure was maintained by metaraminol during the period immediately following the cerebral ischemia.[3] Since metaraminol has both a cardiac inotropic and a peripheral vascular effect, it is possible that neurologic recovery of the animals was a result of improved cerebral perfusion from maintainance of cardiac output and mean arterial pressure in the initial postinjury period.

Summary and Conclusions

Sequential hemodynamic events were observed in a group of patients with head injury throughout their clinical course. Significant hemodynamic changes in the series as a whole were low cardiac output and stroke volume during the early period and return to normal or above during the middle and late periods; there was an initial tachycardia which decreased during successive stages.

In the early period, the patients who did not survive had lower cardiac output, higher peripheral resistance, lower central blood volume, lower stroke volume and lower stroke work than did the survivors. During the middle and late periods, the nonsurviving patients had cardiac outputs, stroke volumes and heart rates similar to those of the survivors.

On the bases of these studies, we postulate that the initial hemodynamic abnormalities of patients with head injury were due to alterations in the central neural regulatory mechanisms and that hemodynamic recovery is dependent upon the intrinsic properties of cardiac muscle as well as recovery of central regulation.

These observations suggest that therapy of patients with head injury should include sympathomimetic agents to maintain cardiac output before hypotension occurs.

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One-Stage Allotransplantation of Both Lungs in the Dog

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HUMAN KIDNEY, liver and heart transplantations rest on an achievement in the laboratory of long-term survival of animals in which these organs were totally replaced by allografts. Such a background for clinical lung transplantation, however, is lacking despite extensive studies of single lung allografts in dogs. The healthy recipient animal, in which one lung is intact, does not need the allograft to remain active. Survival *per se* signifies neither the functional status of the graft nor the efficacy of immunosuppressive measures. In many instances, unilateral lung allografts are retained but with nearly total loss of function.

Study of dogs with allografts of both lungs, therefore, is essential for a better understanding of the events of rejection and development of optimal immunosuppressive methods. Survival of such animals would be much more significant and all the respiratory parameters that can be readily and frequently measured, without the need for the inaccurate and cumbersome procedures of canine bronchospirometry, would largely reflect the degree of rejection damage. Besides, it is now believed that simultaneous transplantation of both lungs will be necessary in emphysema when lung transplantation is indicated.[6] Obtaining long-term survival of animals following this procedure may thus urge clinical lung transplanters to proceed.

We have previously shown the feasibility of one-stage replantation of both lungs with long-term survival of dogs with nearly normal dynamics of ventilation and pulmonary circulation.[1] The next step, allotransplantation, is the subject of the present report.

Methods

We have used 33 pairs of healthy adult mongrel dogs weighing 15–20 Kg. Donors and recipients were approximately of equal size and paired without regard to sex. Anesthesia was light and consisted of intermittent intravenous doses of Surital (thiamylal sodium). A Bird respirator delivering a 40–60 oxygen-air mixture provided control of respirations during operation. The surgical technic was similar to that of one-stage replantation of both lungs which we have previously described in detail.[2] The following is a brief account with emphasis on several points pertinent to the allotransplantation procedure.

The donor and the recipient were anesthetized simultaneously and placed in the left lateral decubitus position. The same surgical team performed both operations. First, through a right thoracotomy the right lung of the donor was completely mobilized but was not removed, so that its blood flow would continue until the recipient was prepared. Then a right thoracotomy was performed on the recipient and the right lung was removed being careful to leave on this animal an adequate cuff of left atrium, and a rather long right pulmonary aterial and right bronchial stump; it is also important to preserve the vagus nerve and peribronchial tissues. The next step was the removal of the donor lung, this time leaving a conveniently long left atrial cuff and pulmonary artery on the lung itself, and the bronchus was divided close to its lobar orifices. The allograft was then perfused with 500 cc. of lactated Ringer's solution at 4°C through its pulmonary artery with a pressure head of 40 cm. of water, while on the donor the left atrium, the pulmonary arterial and the bronchial stumps were being sutured, the vascular clamps removed and the thoracotomy incision was rapidly closed with a few interrupted all-layer sutures. After completion of right lung transplantation the recipient thoracotomy incision was meticulously closed with drainage. For trans-

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plantation of the left lung both dogs were turned to the other side and the recipient pneumonectomy was performed first. Then, 500 cc. of blood was removed from the donor and its left lung was expeditiously removed at the same time sacrificing this animal. The allograft was placed in the recipient and the incision was closed without drainage.

We have usually been able to complete the entire procedure within 3 hours. During the operation 300–500 cc. of blood and 500 cc. of 5% dextrose in water were administered intravenously to the recipient. Reflexes and spontaneous respiratory activity returned within 1 hour of operation and the endotracheal tube was removed. The animals spent the first night in prone position in a special cage with temperature control and into which 5 liters/min. of oxygen were delivered. The next day they were transferred to an ordinary cage. Broad spectrum antibiotics were administered for a week postoperatively.

We have followed the postoperative course of these dogs by frequent chest x-rays, determinations of arterial blood gases and pH, and complete blood counts. We have removed the heart and both lungs as soon after death as was possible and grossly examined both lungs and all the anastomoses. Then, the lungs were inflated with and immersed in formalin solution. Multiple sections from each lung were studied histologically in the pathology department.

To evaluate the effects of immunosuppressive drugs on rejection phenomena we have divided the dogs into three groups: A first group of eight dogs served as controls without any immunosuppressive treatment. A second group of 14 dogs were to receive 5 mg./Kg. azathioprine orally and 20–40 mg. prednisone intramuscularly every day starting from the day of operation until death. A third group of 11 dogs were to receive 0.1 mg./Kg. Methotrexate subcutaneously every other day and 20–40 mg. prednisone intramuscularly every day; the same dose of Methotrexate was to be administere twice a week during the second postoperative wee and once a week thereafter. In the last two groups th dosage of prednisone was to be increased up to 200 m daily and then gradually tapered.

Results

The results are summarized in Table 1. Two dogs ar not included in this table because they died ver shortly after the operation and represented obviou technical failures.

Survival. All eight dogs of the control group survive from 2 to 5 days. One of these dogs died during th second postoperative day with a bronchial leak an another one died on the third postoperative day wit infarction of the cardiac lobe of the right lung due t torsion of the pulmonary arterial branch to this lobe Histologic examination revealed various degrees of rejection and intra-alveolar edema in the allografts of al these dogs.

In the second group (azathioprine and prednisone) four dogs died during the first postoperative day wit severe pulmonary edema and respiratory insufficiency in addition, torsion of a lobar pulmonary arterial branc was observed at autopsy in two of these dogs. Two dog died on the second postoperative day, one with acut gastric dilatation presumably due to intraoperative bilateral damage to vagus nerves, the other of aspiratio of gastric contents to tracheobronchial tree while drinking milk. One dog died on the third postoperative da and the only significant post-mortem finding was a partia left atrial thrombus. The remaining five dogs survive from 4 to 21 days; moderate pulmonary edema and rejection were observed in all except the longest survivo which had pulmonary infection.

In the third group (Methotrexate and prednisone) six dogs died during the first 48 hours; all had pulmonar edema, the pulmonary artery of one was found to b

TABLE 1. *Length of Survival and the Degree of Rejection at Death*

Control			Azathioprine Prednisone			Methotrexate Prednisone		
Dog No.	Survival (days)	Rejection	Dog No.	Survival (days)	Rejection	Dog No.	Survival (days)	Rejection
C-8	2	None	5	1	None	18	1	None
C-6	2	+	6	1	None	9	2	None
C-5	3	++	12	1	None	11	2	None
C-2	3	+++	15	1		16	2	
C-1	4	+++	2	2		20	2	None
C-3	4	+++	8	2		23	2	None
C-7	4	+++	4	3	None	19	5	+
C-4	5	+++	1	4	None	22	5	++
			10	5	+	13	6	++
			7	7	++	21	16	+++
			14	6	++	17	177	+++
			3	21	?			

full of heartworms, another one had a bronchial leak. One dog died during the fifth day with pneumonia. Two dogs, apparently in good condition on the fifth and sixth days, died of acute pulmonary edema while they struggled against restraint on the x-ray table. The remaining two dogs survived 16 and 177 days respectively (Fig. 1). The longest survivor died with late rejection.

Radiologic Findings. Chest x-rays were, as a rule, clear during the first and second postoperative days (Figs. 2 and 3). However, diffuse edema in both lung fields were common x-ray findings subsequently (Fig. 4). That such radiologic pictures were due to edema was frequently verified by post-mortem examinations. Pulmonary edema subsided and disappeared on the three longest survivors after the tenth day (Fig. 5).

Blood Counts. Erythrocyte, leucocyte, platelet counts, differential blood counts, hemoglobin and hematocrit determinations which were frequently performed postoperatively did not appear to be of significant help as a guide in regulating the dosage of immunosuppressive drugs. In dogs under immunosuppressive treatment erythrocyte, hemoglobin and hematocrit values did not change appreciably; leucocyte counts never became low enough to make a decrease in dosage of drugs necessary. A uniform decrease in platelet counts was noteworthy.

Arterial Blood Gas Values and pH. Arterial oxygen tensions significantly declined during the first week after the operation and this was matched by a rise in pH. The carbon dioxide tensions in arterial blood remained normal. In dogs surviving beyond the first week arterial oxygen tensions approached normal levels.

FIG. 1. Three of the dogs several days after one-stage allotransplantation of both lungs. The first from the left survived 177 days.

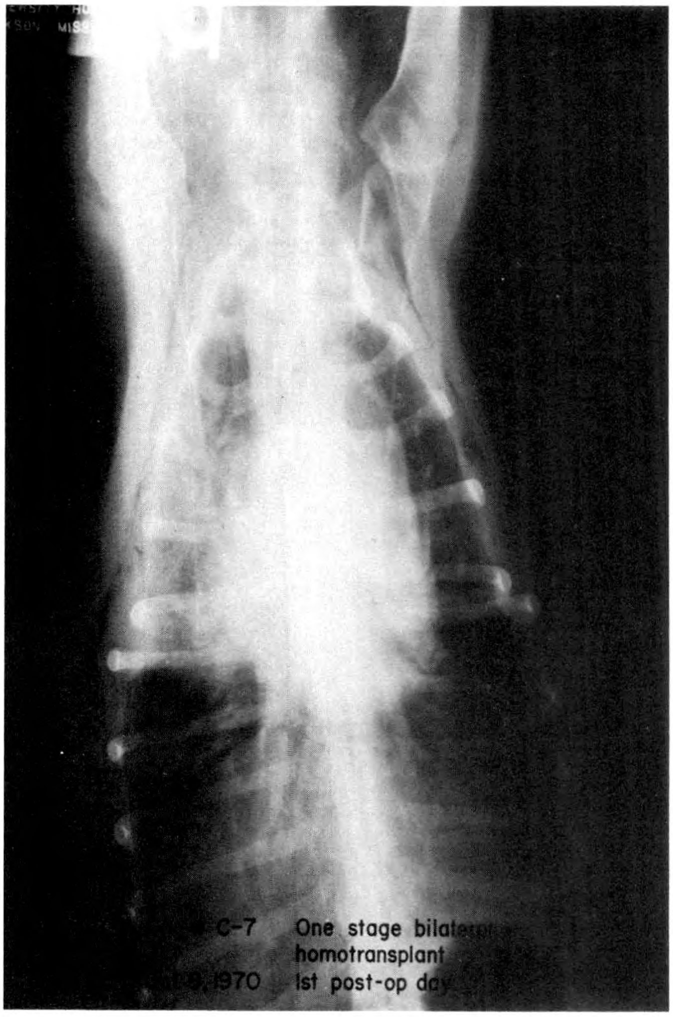

FIG. 2. Chest x-ray of a dog on the first postoperative day.

Post-mortem Findings and Rejection Phenomena. Thrombosis at the left atrial suture line of either lung, compromising its pulmonary venous outflow, occurred only three times. We have not observed pulmonary arterial thrombosis in any of the autopsies. In the bronchial mucosa of the allografts of dogs dying within the first 24 hours, pathologic findings were hyperemia, edema and focal areas of hemorrhage; between the second and seventh days edema, diffuse hemorrhage, epithelial desquamation and necrosis in bronchial mucosa were commonly encountered. Retention of endobronchial secretions was a remarkably infrequent finding. In dogs surviving more than a week we have observed areas of regeneration adjacent to the necrotic areas, in the bronchial mucosa of the allografts. Fatal bronchial leaks occurred in only three dogs of this study. In histologic examination of the allografts we have seen various degrees of intra-alveolar edema along with re-

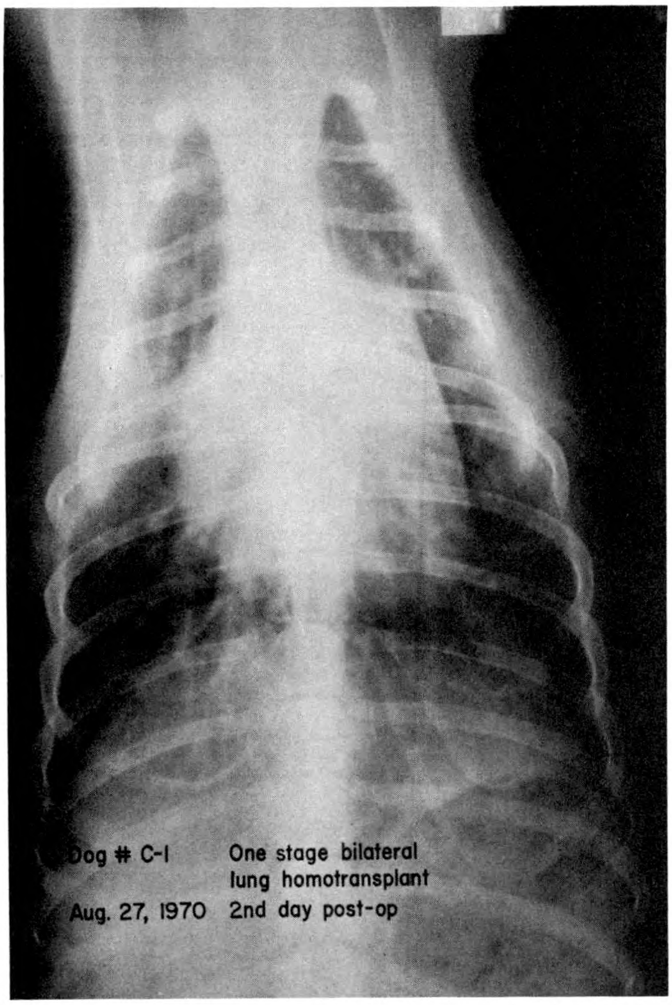

FIG. 3. Chest x-ray of another dog on the second postoperative day.

jection phenomena. In addition, chronic passive congestion and bronchopneumonic areas were present in most of the tissue sections, and occasionally focal hemorrhagic areas were observed.

We have attempted to evaluate the events of rejection by arbitrarily designating three grades to the process depending on the stage of its development (Table 1). Grade (+) includes only the initial evidence of the rejection phenomena consisting of a slight but definite perivascular accumulation of mononuclear cells (lymphocytes with a scattering of plasma cells) about the smaller blood vessels, usually peripherally located in the lobe. This was associated with extensive intra-alveolar edema and, in some areas, with inter-alveolar hemorrhage. Grade (+++) is characterized by extensive infiltration of similar cells not only about the smaller blood vessels but also about the larger vascular structures and the smaller bronchi. There was extensive loss of bronchial epithelium, and plugging of bronchi with an apparent mixture of mucus and fibrin. The alveolar septa were edematous, congested and contained large numbers of alveolar macrophages. A protein precipitate lined the alveoli in some areas, suggesting the microscopic appearance of hyaline membrane disease. A pleural reaction of fibrin precipitate, with early organization and with a distinct layer of mononuclear cells beneath, was frequently seen. This was associated with the gross finding of a hemorrhagic pleural effusion. Grade (++) represents the stage of development in the rejection process midway between grades (+) and (+++). The boundaries are poorly defined and, of course, depend upon a subjective estimation of the degree of the rejection process.

No histologic differences were noted in the rejection process in the animals treated with immunosuppressive drugs and the untreated control group. The only difference was the rapidity of its development in the control group.

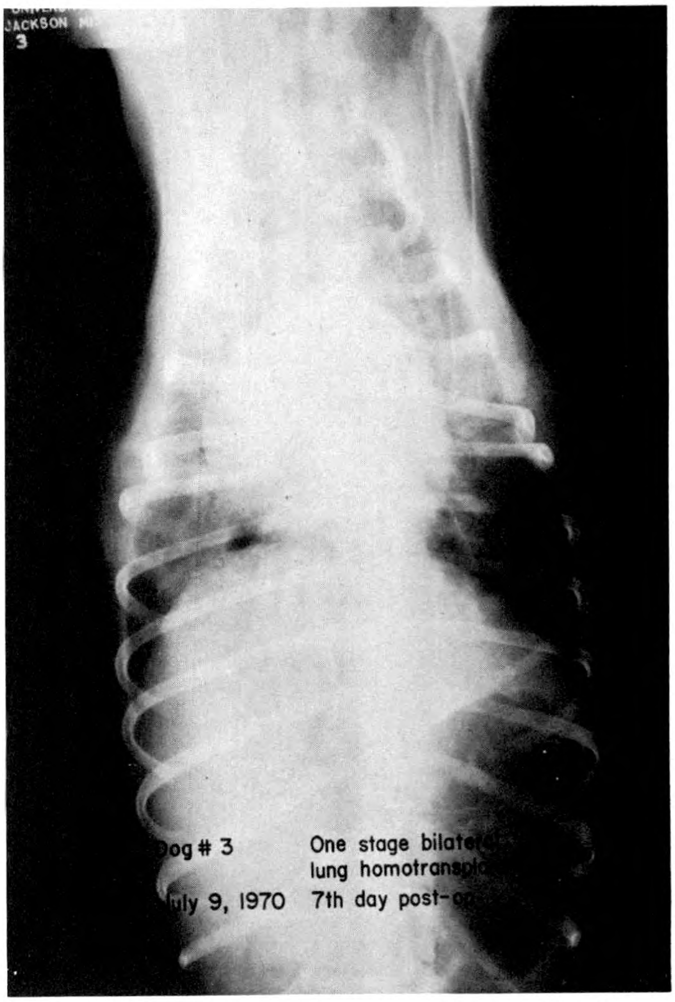

FIG. 4. Chest x-ray of a dog 7 days after the operation showing diffuse edema in both lung fields.

Discussion

Technical Considerations. We had ascertained the adequacy of the surgical technic to be used in these experiments during our previous one-stage bilateral replantation experiments[1,2] in which the complicating issue of immunologic rejection was absent. Thirty-eight per cent of dogs subjected to an operation of this magnitude had survived more than a month. In many of them lung scans, pulmonary angiograms, pulmonary arterial pressures and arterial blood gas values were within normal limits several months after the procedure. Some of these dogs are alive and active now more than 2 years after operation. Although potential adverse effects of denervation and interruption of bronchial arteries and lymphatics still await full clarification, our replantation studies had thus corroborated that such effects by themselves were not so serious as to preclude ong-term survival of dogs.

In undertaking the present study, therefore, we were well familiar with problems of a purely technical nature. A very important one among these was the occurrence of from mild to severe pulmonary edema most probably due to anoxic damage inflicted upon he graft during the act of removal and replacement.[1,2] This potentially reversible pulmonary edema was frequently observed to be a chief cause of early deaths ollowing allotransplantation also.

Although the dogs were usually eager to eat during he first postoperative day, if allowed to do so, there was a strong tendency to vomit and aspirate the gastric ontents into the bronchial tree while eating. Another omplication is gastric dilatation due to bilateral vagal njury. A serious complication occurs as a result of faulty placement of some of the lobes of the allograft in the horacic cavity; rotation of especially the right lower and he left upper lobe arteries must be meticulously avoided o prevent hemorrhagic infarcts of these lobes.

Respiratory Pattern. In most of the dogs, respirations were deep and slow for one or two days after operation.[1] n some of the animals, however, we observed a rapid ate of respiration very shortly after return of spontaneus respiratory activity. Such dogs usually had a comlication (pneumothorax, intrapleural bleeding, atelecasis or pulmonary infarct). Sometimes we were able to nduce panting, rapid and shallow respirations with a requency of up to 100/min., only a few hours postperatively by heating the dog's cage to 30–35°C. At the eginning of the study we attempted to make use of his point in shortening the period of adaptation of the og to total pulmonary denervation. Later, we disconnued this practice because it was uncertain whether or ot panting increased alveolar ventilation. Furthermore, anting started only after transudation of some fluid into the alveoli; it might, therefore, facilitate the development of pulmonary edema. Conversely, it appeared that keeping the dogs in a cool environment decreased the tendency for pulmonary edema.

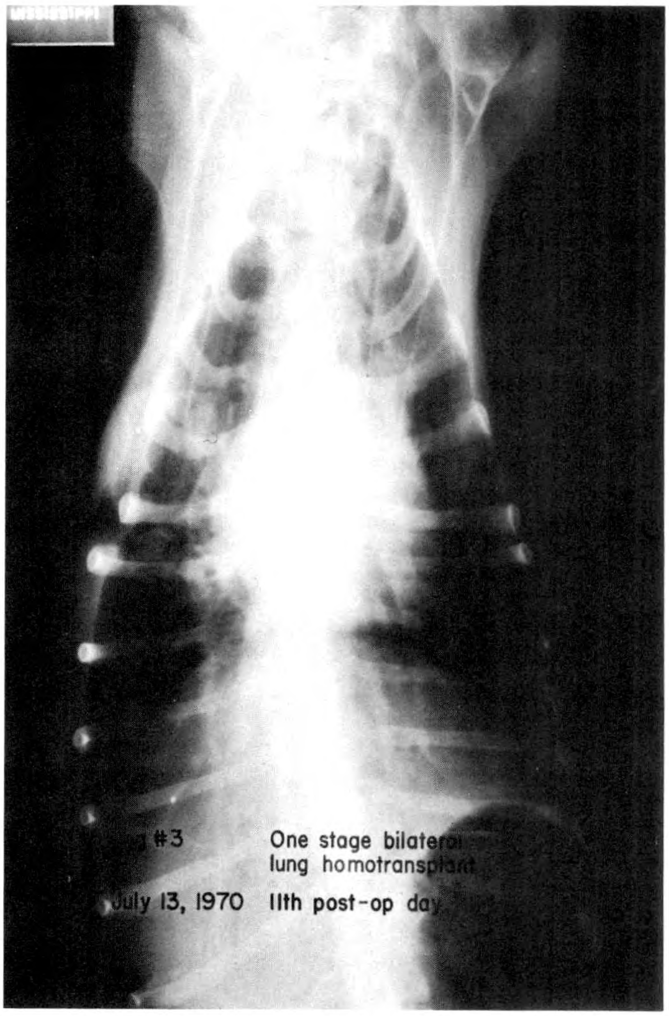

FIG. 5. This chest x-ray and the one in Figure 4 belong to the same dog; this was taken a few days later when both lung fields became clear. This dog died of infection on the 21st day with questionable histologic evidence of rejection.

Rejection and Immunosuppression. Microscopic examination of the allografts has shown that rejection phenomena became discernible almost invariably on the second or third day after the operation. This coincides with post-transplantation pulmonary edema.

Dogs of the control group, without immunosuppression, did not survive more than 5 days. This experience is similar to that of Veith and associates[5] who performed allotransplantation of both lungs at one operation on 15 dogs. Ten of their dogs which recovered from anesthesia survived 2 to 5 days; death resulted from allograft rejection and pneumonia. This period is considerably shorter than that usually reported as the length of survival of untreated recipients of unilateral lung allografts. It is remarkable that hemorrhagic necrosis as described for unilateral lung allografts by Flax and associates[3] was not seen in our experiments. Probably, the bilaterality of the reaction caused pulmonary insufficiency of such a degree that the animals died before this far advanced stage of rejection was reached. On the other hand, the recipients of unilateral allografts die not of pulmonary insufficiency but of the systemic effects of hemorrhagic, necrotic and degenerative pulmonary lesions. There is no reason, therefore, for attributing shorter survival with bilateral lung allografts to the large antigenic tissue influencing the immunologic response of the host.

Immunosuppressive treatment prolonged survival but various grades of rejection ultimately occurred. In the "azathioprine and prednisone" group, three out of 12 dogs survived more than 5 days, the longest survival being 21 days. In the "Methotrexate and prednisone" group, three out of 11 dogs survived more than 5 days, the longest survival being 177 days.

Veith and associates[4] have recently described an intra-alveolar phase in lung rejection characterized by filling of the alveoli by a protein precipitate. They believed that this phase was also observed in some of the clinical cases. However, it is open to question whether or not this protein substance is directly related to immunologic reaction. In our experience, although intra-alveolar edema was common, protein precipitate was rather rarely encountered. We believe that the contents of intra-alveolar edema fluid might change into a protein precipitate when infection is superimposed on post-transplantation edema.

In conclusion, this study shows that long-term surviv
following one-stage allotransplantation of both lungs i
the dog is possible. To obtain long-term survival co
sistently, however, improved methods of immunosu
pression and means to diagnose rejection in its earlie
stages are needed.

Summary

We have performed one-stage allotransplantation o
both lungs in 33 dogs. Eight dogs serving as an u
treated control group died of pulmonary edema an
early rejection within 2 to 5 days. Immunosuppressiv
treatment in the remaining dogs prolonged survival bu
various degrees of rejection ultimately occurred; thre
longest survivors lived 16, 21, and 177 days.

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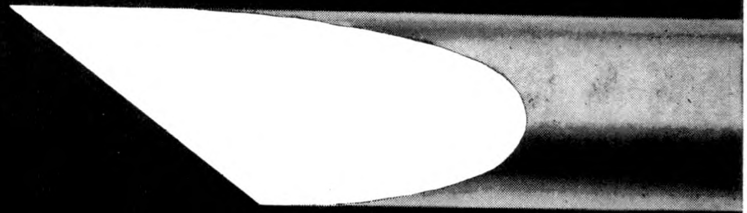

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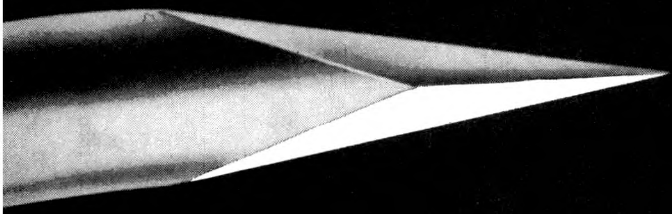

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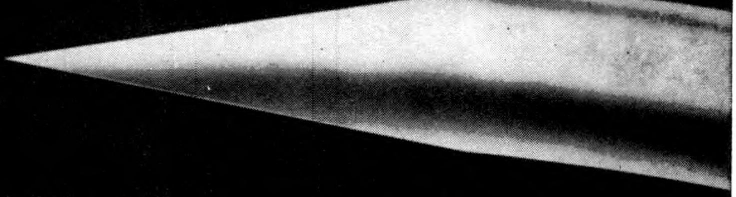

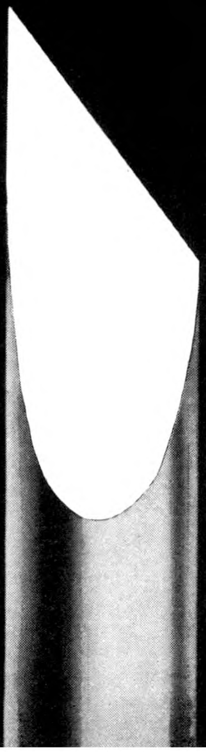

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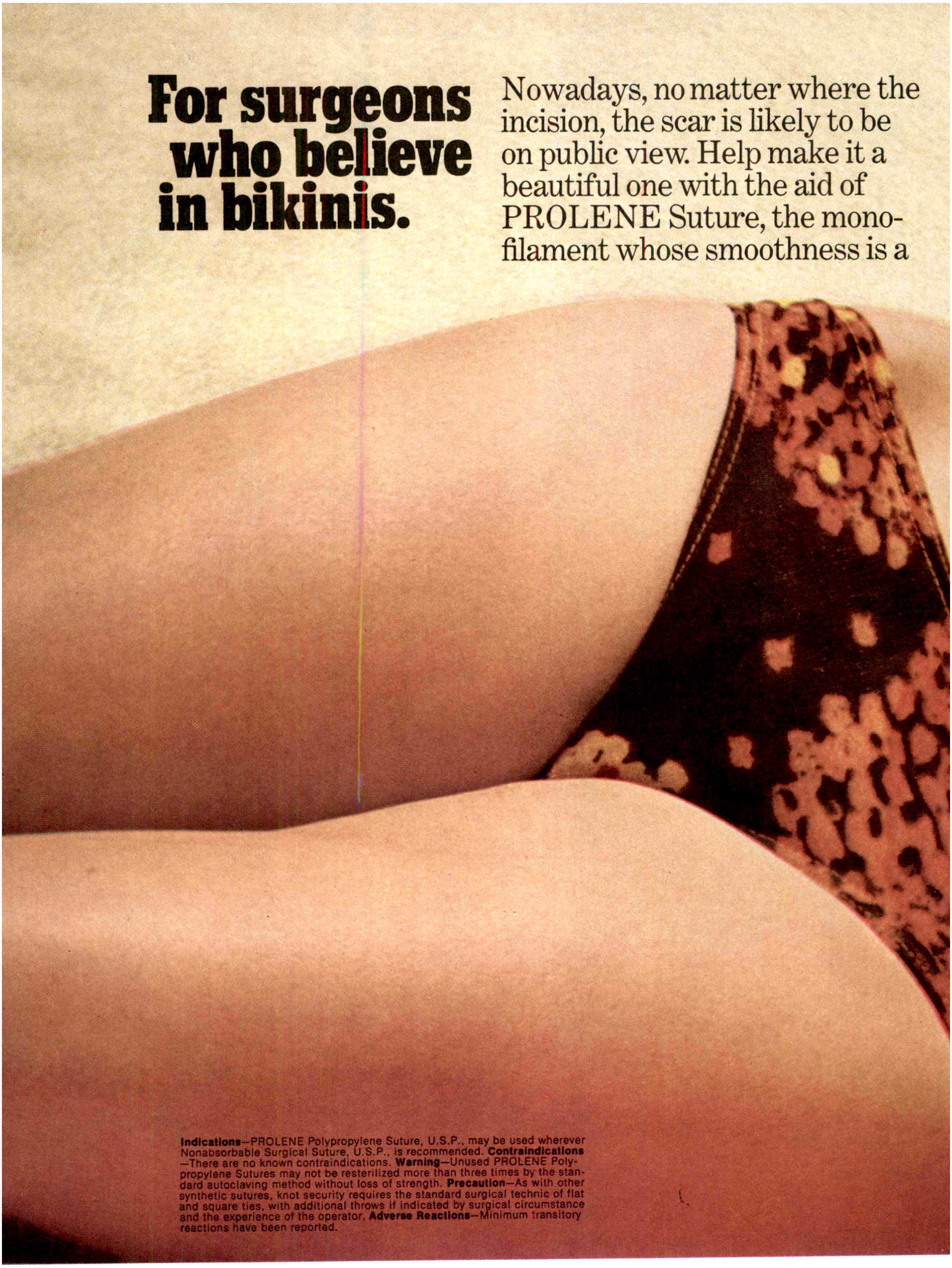

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Indications—PROLENE Polypropylene Suture, U.S.P., may be used wherever Nonabsorbable Surgical Suture, U.S.P., is recommended. **Contraindications**—There are no known contraindications. **Warning**—Unused PROLENE Polypropylene Sutures may not be resterilized more than three times by the standard autoclaving method without loss of strength. **Precaution**—As with other synthetic sutures, knot security requires the standard surgical technic of flat and square ties, with additional throws if indicated by surgical circumstance and the experience of the operator. **Adverse Reactions**—Minimum transitory reactions have been reported.

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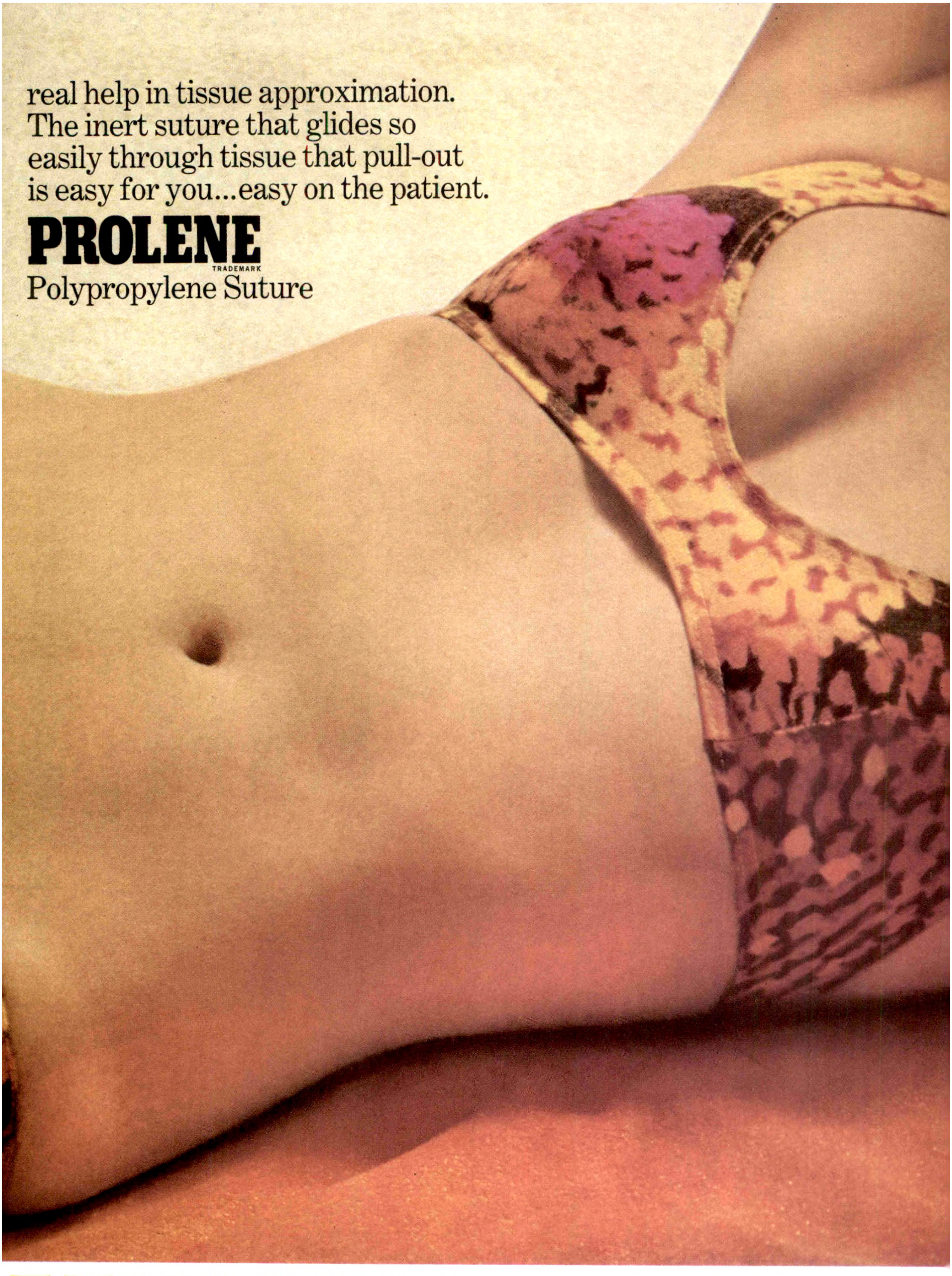

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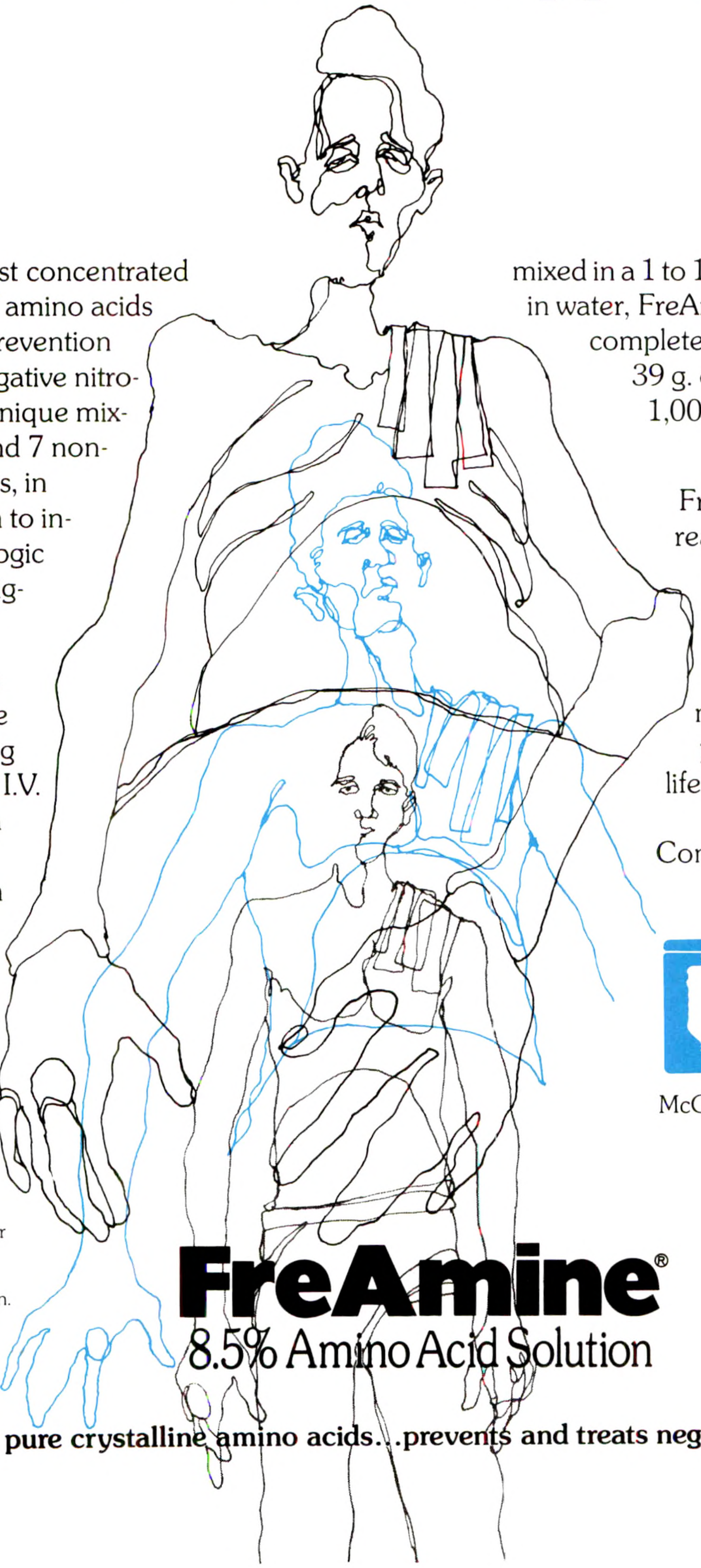

When life hangs on protein intake… FreAmine® is life-supportive.*

FreAmine is the most concentrated parenteral source of amino acids obtainable for the prevention and treatment of negative nitrogen balance. It is a unique mixture of 8 essential and 7 nonessential amino acids, in pure crystalline form to insure immediate biologic availability without significant waste.

FreAmine promotes anabolism and tissue synthesis even during extended periods of I.V. nutrition. Its formula is based on the two international protein standards. When mixed in a 1 to 1 ratio with 50% dextrose in water, FreAmine provides 6.25 g. of completely utilizable nitrogen and 39 g. of protein equivalent per 1,000 ml, plus 850 total nonprotein calories.

FreAmine is furnished in a ready-to-mix kit containing everything necessary for basic hyperalimentation, including 50% dextrose in water. Find out more about how McGaw puts it all together—with life-supporting I.V. nutrition in convenient kit form. Contact your McGaw representative or write for free brochure.

McGaw puts it all together.

FreAmine®

8.5% Amino Acid Solution

Supports life with pure crystalline amino acids…prevents and treats negative nitrogen balance.*

*With adequate calories and other nutrients, when oral alimentation is not feasible for prolonged periods and/or there is impaired gastrointestinal absorption of protein.

DESCRIPTION: Each 100 ml. contains: FreAmine Amino Acid Mixture*, 8.5 g.; Sodium Bisulfite, U.S.P., less than 0.10 g.; Water for Injection, U.S.P., q.s., pH adjusted with acetic acid (approximately 20 mEq./1. Acetate).
Approximate concentration of amino acids (g./100 ml.):

Essential Amino Acids: L-Isoleucine 0.59; L-Leucine 0.77; L-Lysine HCl 0.77; Methionine 0.45; L-Phenylalanine 0.48; L-Threonine 0.34; L-Tryptophan 0.13; L-Valine 0.56.

Nonessential Amino Acids: L-Alanine 0.60; L-Arginine 0.31; L-Histidine 0.24; L-Proline 0.95; L-Serine 0.50; Aminoacetic Acid (Glycine) 1.8; L-Cysteine • HCl • H_2O <0.02. Alpha amino nitrogen greater than 80% of total nitrogen present. Concentration of Electrolytes (mEq./1.): Sodium 10, Chloride 45.

8.5% FreAmine Solution is a sterile, nonpyrogenic solution containing pure crystalline amino acids. A 500 ml. unit provides a total of 39 g. of protein equivalent and 6.25 g. of nitrogen.

ACTIONS: 8.5% FreAmine Solution provides, in concentrated form, a physiological ratio of completely utilizable amino acids for protein synthesis. Used with concentrated carbohydrate solutions, e.g., 20 to 50% dextrose solutions, as a source of calories plus electrolytes and vitamins, it provides total parenteral nutrition.

INDICATIONS: As an adjunct in the prevention of nitrogen loss, or in the treatment of negative nitrogen balance in patients where: (1) oral alimentation is not feasible for prolonged periods, and (2) there is impaired gastrointestinal absorption of protein.

CONTRAINDICATIONS: 1. Anuria; 2. Hepatic coma.

WARNINGS: 1. Administration of amino acids to a patient with hepatic insufficiency may result in a rise in blood ammonia. 2. Administration of amino acids in the presence of impaired renal function may augment an increasing blood urea nitrogen. 3. It is essential to provide adequate calories if parenterally administered amino acids are to be retained by the body and utilized for protein synthesis. Calorie-to-nitrogen ratios of 125 to 150 calories per gram of nitrogen have been recommended to achieve positive nitrogen balance in traumatized patients, for example, surgical cases. 50% Dextrose in Water is a convenient source of adequate calories. 4. FreAmine has not been used in pregnant women; therefore, its safe use in such patients has not been demonstrated.

PRECAUTIONS: 1. Whenever possible, 8.5% FreAmine Solution and its associated calorie solution should be administered through an indwelling intravenous catheter with the tip located in the vena cava or right atrium. 2. During prolonged therapy, clinical evalution and periodic laboratory determinations are necessary.

ADVERSE REACTIONS: Rarely, minor local reactions consisting of a warm sensation and erythema when the solution is administered by peripheral vein.

DOSAGE AND ADMINISTRATION: The total daily dose of 8.5% FreAmine Solution depends on daily protein requirements and on the patient's response, which is determined by clinical judgment aided by such laboratory data as nitrogen balance and serum protein levels. Recommended daily allowances of protein are approximately 0.9 g. (12 ml.**) per kg. of body weight for a healthy adult and 1.4 to 2.2 g. (18 to 28 ml.**) per kg. for healthy growing infants and children. Thus, doses of 370 ml. and 840 ml. of 8.5% FreAmine Solution would provide the recommended daily allowances of protein for a normal 16 kg. (35 lb.) child and 70 kg. (154 lb.) adult respectively.

Protein requirements in traumatized or malnourished patients may, however, be substantially increased. The determination of nitrogen balance is probably the best means of accurately assessing individual protein requirements. Daily doses ranging from 15 to 24 ml. (1.2 to 1.9 g.) per kg. of body weight are generally sufficient in such patients to satisfy protein needs and promote positive nitrogen balance although up to 45 ml. per kg. have been administered in special cases.

For optimum amino acid retention and utilization, 8.5% FreAmine Solution should be administered at a rate of approximately 1 ml. per kg. of body weight per hour. At this rate a 70 kg. patient would receive 500 ml. in an eight-hour period. The administration rate should never exceed 2 ml. per kg. per hour.

Whenever possible, 8.5% FreAmine Solution and its associated calorie solution should be administered through an indwelling intravenous catheter with the tip located in the vena cava or right atrium.

ROUTE: Intravenous.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

HOW SUPPLIED: 8.5% FreAmine Solution is supplied sterile and nonpyrogenic in 500 ml. intravenous infusion bottles.

*Crystalline amino acid mixture, isolated and purified from edible soybean hydrolysate or synthesized.

**Based on protein equivalent of 39 g. per 500 ml. of 8.5% FreAmine Solution.

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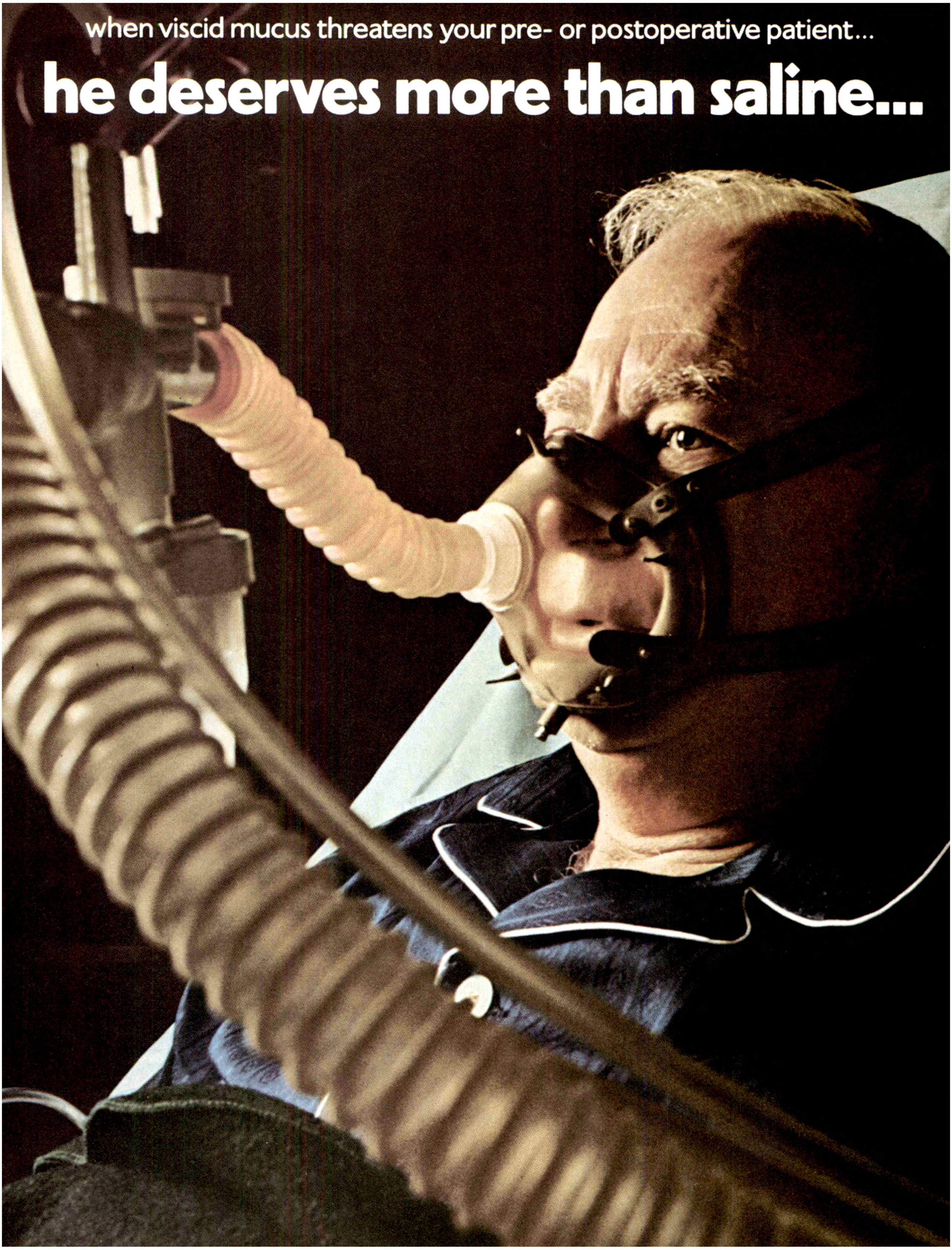
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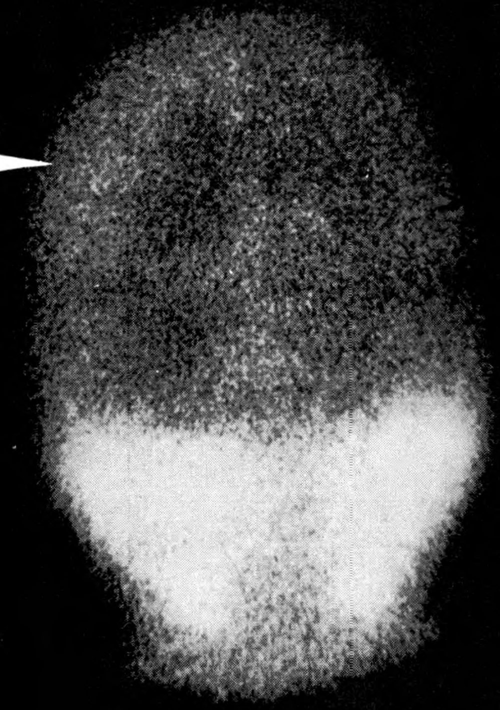
intracerebral or subdural hematoma?*



*A subdural hematoma is revealed in this posterior radioisotope brain scan. The increased activity is noticeable over the left lateral vertex of the skull. During surgery, a large subdural hematoma was evacuated from the parietal area.
Brain scan: Courtesy Harry S. Truman Laboratory, Kansas City, Missouri.

After surgery, when nutritional supplementation is indicated

Berocca® tablets is therapy

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No odor.
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Folic acid	0.5 mg
Ascorbic acid	500 mg

Indications: Nutritional supplementation in conditions in which water-soluble vitamins are required prophylactically or therapeutically.
Warning: Not intended for treatment of pernicious anemia or other primary or secondary anemias. Neurologic involvement may develop or progress, despite temporary remission of anemia, in patients with pernicious anemia who receive more than 0.1 mg of folic acid per day and who are inadequately treated with vitamin B_{12}.
Dosage: 1 or 2 tablets daily, as indicated by clinical need.
Available: In bottles of 100.

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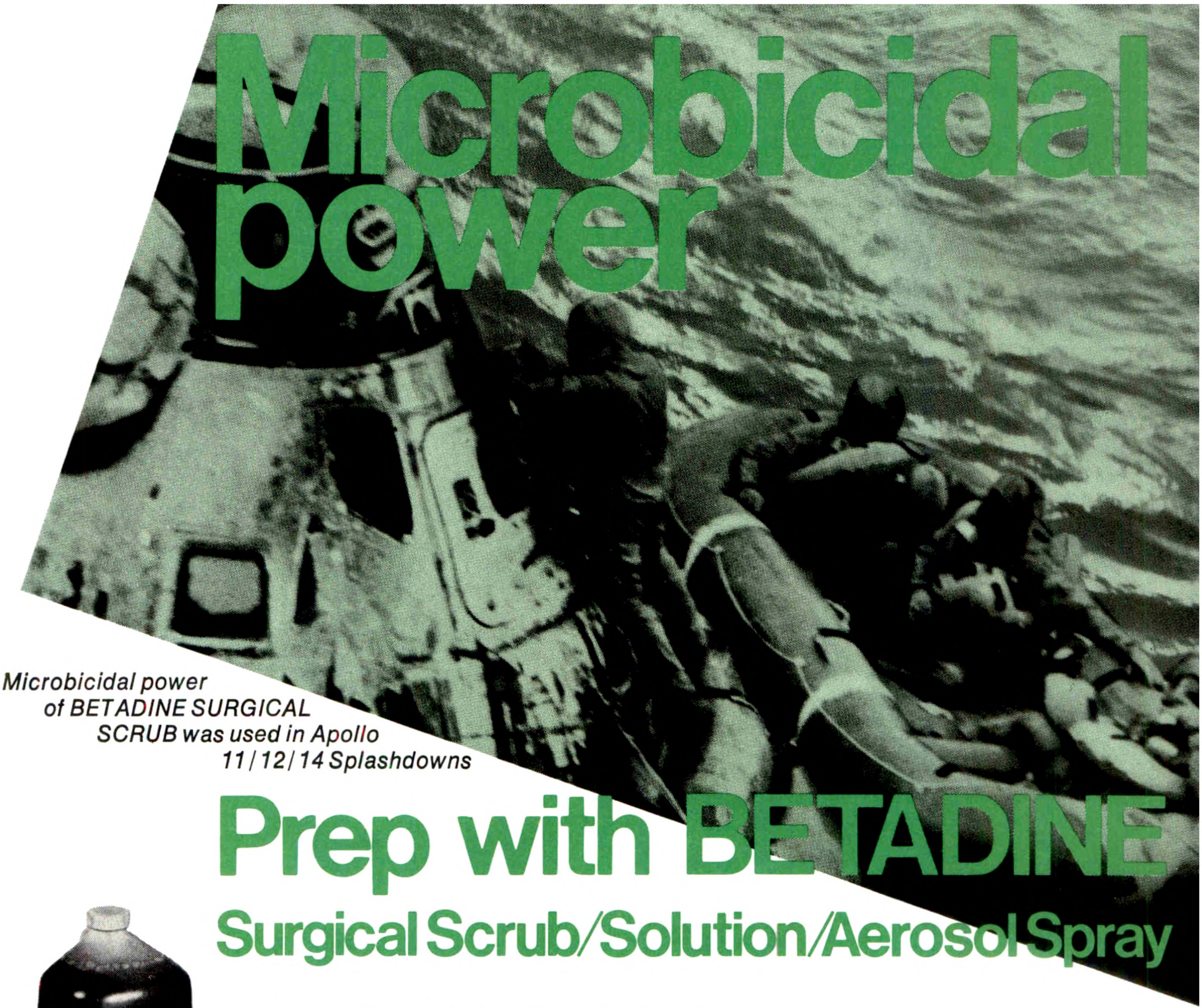

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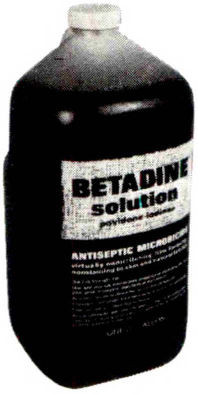

Enhance antisepsis with BETADINE SOLUTION or BETADINE AEROSOL SPRAY—After prepping the operative site with BETADINE SURGICAL SCRUB, paint with BETADINE SOLUTION or spray with BETADINE AEROSOL SPRAY. Both are fully microbicidal, film-forming, exert longer microbicidal action than iodine tincture, and maintain microbicidal action in the presence of blood, pus, serum or necrotic tissue. The site of application can be bandaged or taped.

To help prevent postoperative infection—Reapply BETADINE SOLUTION or BETADINE AEROSOL SPRAY after suturing and during redressing. BETADINE microbicides are virtually nonirritating and do not stain skin or natural fabrics. In the rare instance of local irritation or sensitivity to BETADINE SURGICAL SCRUB, discontinue use in the individual.

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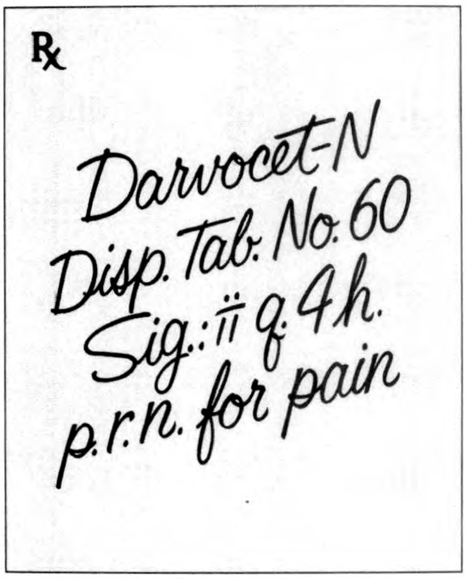
Indicated for the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever



℞

Darvocet-N
Disp. Tab. No. 60
Sig.: ii q. 4 h.
p.r.n. for pain

Usual dosage:
2 tablets q. 4 h.
p.r.n. for pain

Description: Each tablet of Darvocet-N™ (propoxyphene napsylate with acetaminophen, Lilly) contains 50 mg. propoxyphene napsylate and 325 mg. acetaminophen.

Actions: Propoxyphene napsylate is a mild analgesic structurally related to the narcotic analgesic methadone. Though propoxyphene's general pharmacologic properties are those of the narcotics as a group, it does not compare with them in analgesic potency.

Darvocet-N also contains the non-narcotic antipyretic-analgesic acetaminophen.

Indication: Darvocet-N is indicated for the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychosis and convulsions.

[111472]

Additional information available to the profession on request.
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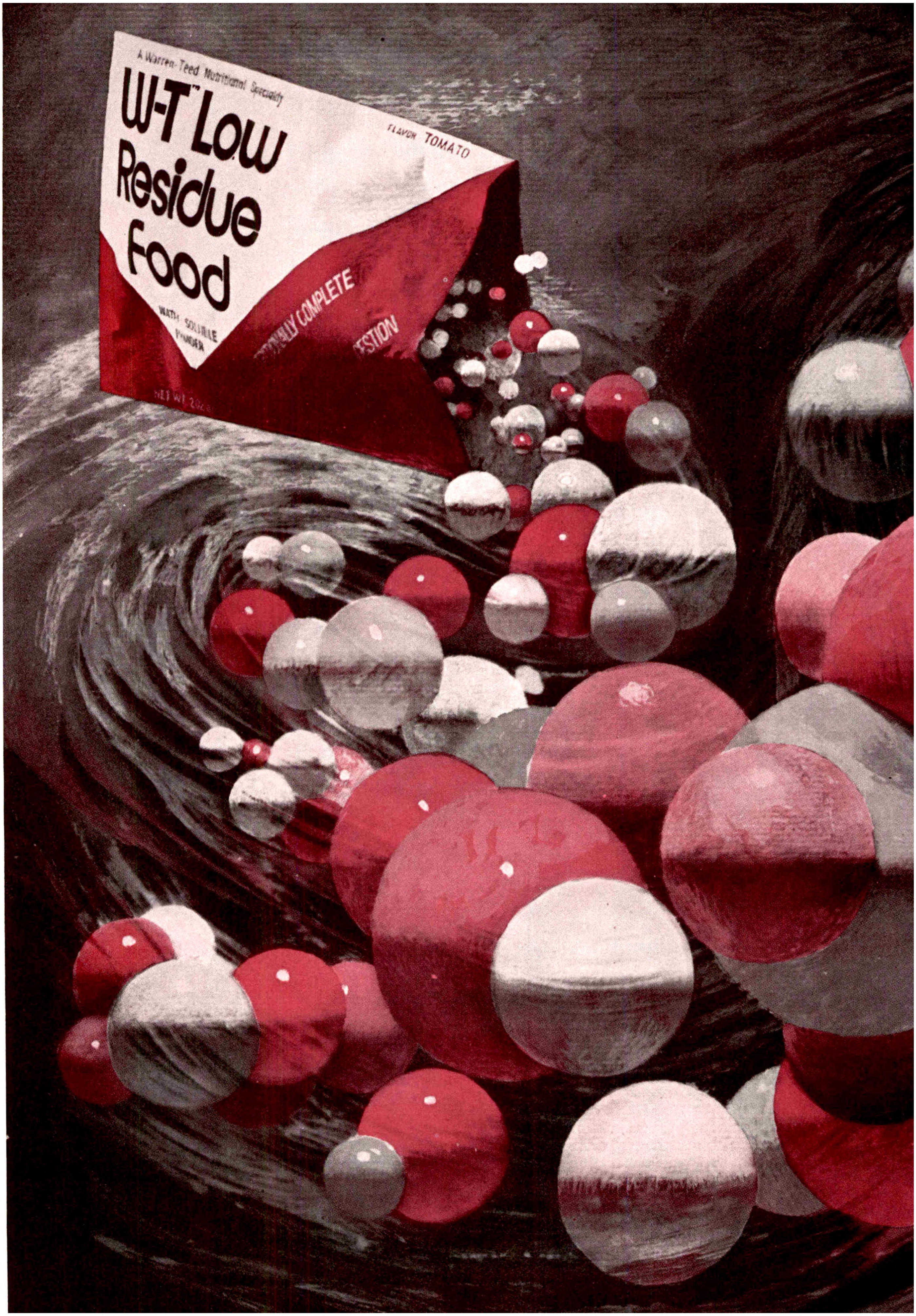
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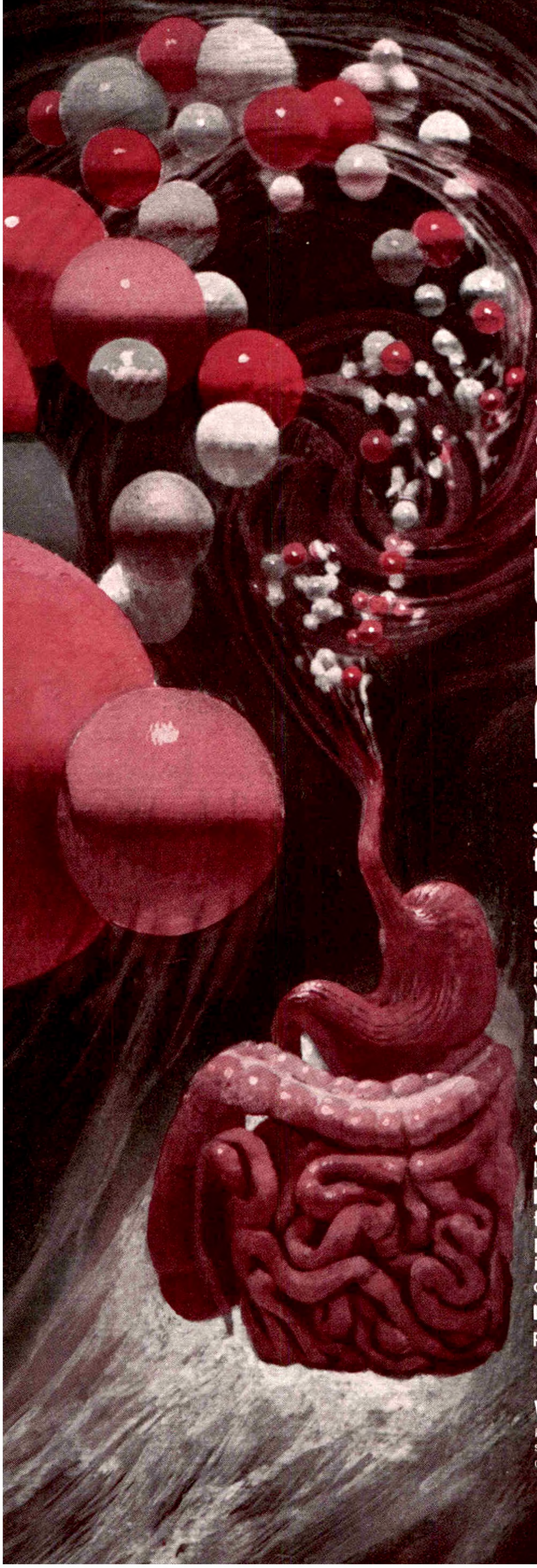

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You can even administer Phenergan IM or IV.†

Phenergan. Versatile.

INJECTION

PHENERGAN®

(PROMETHAZINE HCl)

*Because Phenergan adds to the sedative effects of CNS depressants, including narcotics, such agents should either be eliminated or used in reduced dosage in the presence of promethazine.

rip a smooth one.

ications: Promethazine HCl injection is indicated when the oral form
mpractical for: Amelioration and prevention of allergic reactions to
od or plasma in patients with known history of such reactions; in
aphylaxis as an adjunct to epinephrine and other standard measures
er acute symptoms have been controlled; for other uncomplicated
ergic conditions of the immediate type when oral therapy is impossible
contraindicated; active treatment of motion sickness; preoperative,
stoperative and obstetric (during labor) sedation; prevention and con-
l of nausea and vomiting associated with certain types of anesthesia
d surgery; as an adjunct to analgesics to control postoperative pain;
sedation and relief of apprehension and to produce light sleep from
ich the patient can be easily aroused; intravenously in special surgical
ations (e.g. repeated bronchoscopy, ophthalmic surgery, poor-risk
ients) with reduced amounts of meperidine as adjunct to anesthesia
d analgesia.

ntraindications: Contraindicated in individuals with known hyper-
sitivity to promethazine. Intra-arterial injection is contraindicated.

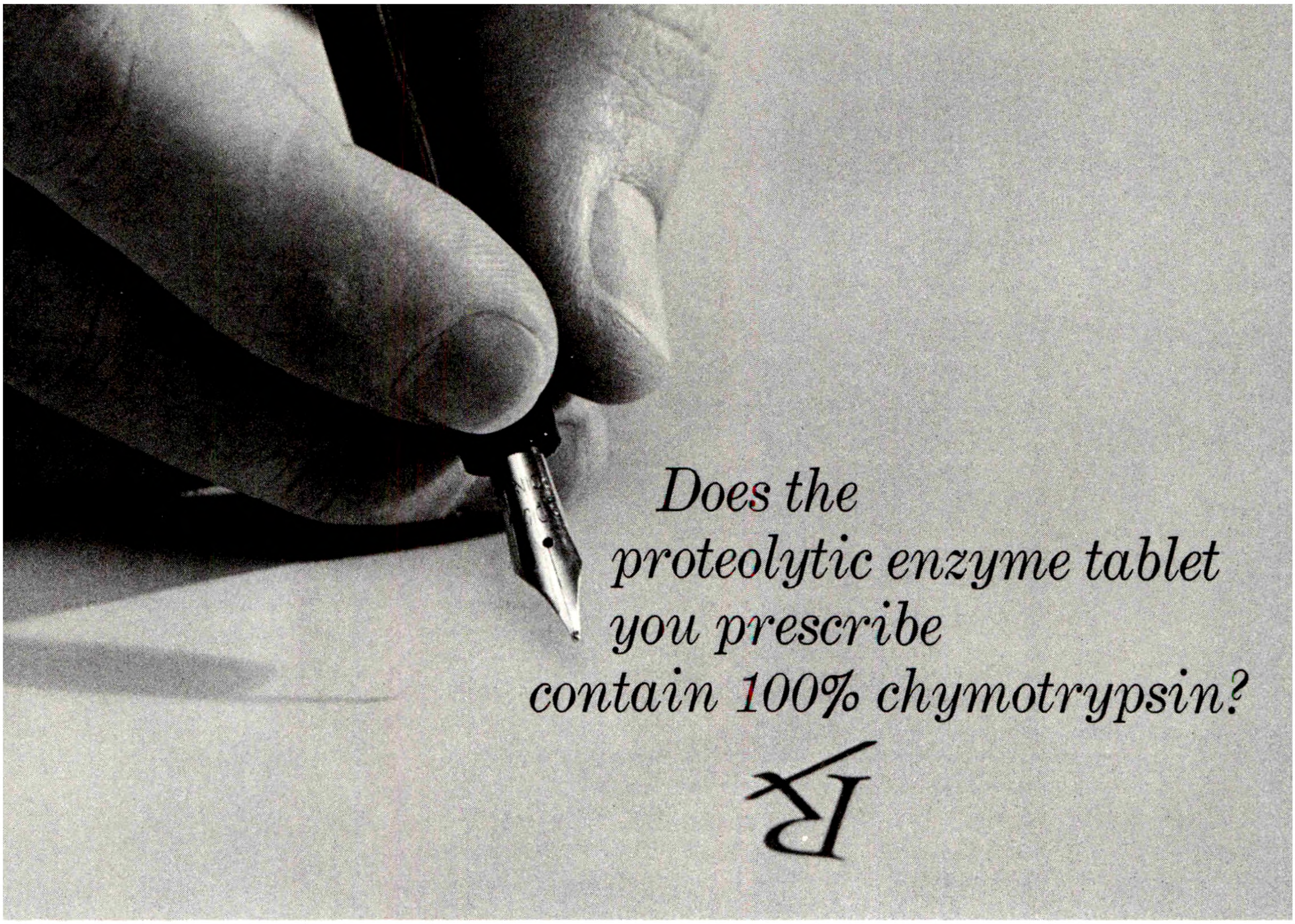
rnings: The sedative action of promethazine is additive to the sedative
ects of CNS depressants; therefore, agents as alcohol, barbiturates
d narcotic analgesics should be eliminated or given in reduced dosage
presence of promethazine. When given concomitantly with pro-
thazine reduce dose of barbiturates by at least ½ and dose of anal-
ic depressants (e.g. morphine or meperidine) by ¼ to ½. Although
per IV use of promethazine is well-tolerated, exercise care not to
w perivascular extravasation since under such circumstances chemi-
irritation may occur.† When used IV, give in a concentration no greater
n 25 mg./cc. and at a rate not over 25 mg./minute.

cautions: Caution ambulatory patients against driving autos or operat-
dangerous machinery until it is known that they do not become
wsy or dizzy from promethazine. Antiemetics may mask symptoms of
ecognized disease and thus interfere with diagnosis. Patients in pain
o received inadequate or no analgesia have developed "athetoid-
" movements of the upper extremities following parenteral prometha-
e. These symptoms usually disappear on adequate control of pain.

verse Reactions: Patients may occasionally complain of autonomic
ctions, e.g. dryness of mouth, blurring of vision and rarely dizziness.
y rare cases have been reported where patients receiving prometha-
e developed leukopenia. In one instance agranulocytosis has been
orted. In nearly every instance reported other toxic agents known to
e caused these conditions were associated with administration of
methazine. Cardiovascular by-effects from promethazine have been
e (minor increases in blood pressure, occasional mild hypotension).
otosensitivity (extremely rare) contraindicates further use of pro-
thazine or related drugs. Attempted suicides with promethazine
ulted in deep sedation, coma, rarely convulsions and cardiorespira-
y symptoms compatible with depth of sedation. A paradoxical reaction
perexcitability and nightmares) has been reported in children receiv-
large single doses.

nposition: Injection—1 cc. ampuls of 25 mg./cc. and 50 mg./cc. Each
also contains 0.1 mg. disodium edetate, 0.04 mg. calcium chloride and
more than 0.25 mg. sodium metabisulfite and 5 mg. phenol with so-
n acetate buffer.

eth Laboratories **Philadelphia, Pa.**



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After 30 minutes in human intestinal juice "63% of chymotryspin was still enzymatically active, whereas only 8% of the original trypsin activity could be detected."[1]

So if you're not getting the results you want from oral proteolytic enzymes, try the only all-chymotrypsin tablet. AVAZYME® (crystalline chymotrypsin–20 mg.) and double-strength AVAZYME®-100 (crystalline chymotrypsin – 40 mg.).

1. Wohlman, A. et al: Proc. Soc. Exp. Biol. & Med., 109: 26, 1962.

AVAZYME®: Each yellow tablet contains 20 mg. of crystalline chymotrypsin equivalent in proteolytic activity to 50,000 Wampole units (20,000 N.F. Units). The tablets have a special enteric coat to insure release in the intestine.

INDICATIONS

Based on a review of this drug by the National Academy of Sciences — National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Relief of symptoms related to episiotomy.

Lack of substantial evidence of effectiveness: Adjunctive therapy for the resolution of inflammation and edema resulting from serious accidental trauma or surgical trauma.

Final classification of the less-than-effective indications requires further investigation.

ACTION: The experimental evidence for the anti-inflammatory action of chymotrypsin and other orally administered anti-inflammatory enzymes is based on animal studies.

CONTRAINDICATIONS: This drug is contraindicated in patients with a history of a prior allergic reaction to chymotrypsin.

WARNING: USE IN PREGNANCY — Safe use of this drug during pregnancy has not been established.

ADVERSE REACTIONS: An occasional patient may experience nausea, vomiting, diarrhea, and skin rash.

DOSAGE AND ADMINISTRATION: In mild conditions, one tablet four times daily. For more severe conditions, two tablets four times daily. There are no known incompatibilities.

DISCUSSION OF CLINICAL USE: Controlled clinical studies have demonstrated the anti-inflammatory action of Avazyme (Crystalline Chymotrypsin) in cases of urologic surgery, episiotomy, and surgery of the head and neck. Corroborative evidence in support of the clinical efficacy has been obtained upon treatment of inflammatory conditions resulting from surgical and accidental trauma.

ALSO AVAILABLE: AVAZYME®-100. White tablets containing crystalline chymotrypsin equivalent in proteolytic activity to 100,000 Wampole Units (approximately 40 mg.).

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AV100 AD-2 2/73

Effect of Acute Progressive Hypoxemia on Cardiac Output and Plasma Excess Lactate

KIRTLAND E. HOBLER, M.S., M.D.,[*] LARRY C. CAREY, M.D.[**]

From the Department of Surgery, Marquette University, Milwaukee, Wisconsin, at the Allen Bradley Medical Science Laboratory

During the Viet Nam conflict, prompt medical evacuations have permitted many patients to be rapidly resuscitated from profound shock. In some of these patients, restoring cardiac output, blood pressure, etc., to normal has been followed by persistently elevated blood lactates. Many of these patients have, in addition, hypoxemia due to congestive atelectasis or other pulmonary problems. Is this lactic acidosis due to hypoxemia, to inadequate perfusion, or to a combination of both? How low must Pa_{O_2} fall before metabolic and circulatory effects result?

An experiment was designed in which dogs were subjected to acute progressive hypoxemia while dye dilution cardiac output and excess lactate were monitored simultaneously. If excess lactate accumulates before cardiac output falls, then it is possible to get some insight into the importance of arterial oxygen tension as an isolated determinant of lactate production and anaerobic metabolism.

Methods

Ten dogs weighing 18 ± 1.2 Kg.[*] were anesthetized with 100 mg./Kg. of chloralose intravenously. The right atrium was catheterized via the femoral vein for central venous pressure (CVP), O_2 saturation, and indocyanine dye injections. The abdominal aorta was catheterized via the femoral artery for B.P., dye detection, Pa_{CO_2}, pH, Pa_{O_2}, O_2 saturation, pyruvate and lactate. Cardiac output, $\dot{Q}$, was determined every 2.5–5 minutes by a single injection of 2 ml. (1.25 mg.) of indocyanine green through the venous catheter. Arterial blood was then drawn by a Harvard pump through a Gilford model DTL densitometer cuvette. Dye accumulation was nulled by using the densitometer zero suppression circuit.

All blood determinations were begun within 1 to 2 minutes of sampling. Lactates were determined by the method of Barker and Summerson,[2] and pyruvates by the method of Friedman and Haugen.[4] Excess lactate, XL, was calculated according to the formula

$$XL = dL - (dP)\ (L/P),$$

in which dL is change in lactate from control, dP is change in pyruvate from control, and L/P is the control lactate/pyruvate ratio.[5] Buffer base deviation was determined with a Sigaard-Andersen nomogram corrected for unsaturation. P_{O_2}, P_{CO_2}, and pH were determined by the appropriate electrodes, while O_2 saturations were determined photometrically by an American Optical Co. oximeter. O_2 consumption, $\dot{V}_{O_2}$, was obtained according to the following formula

$$\dot{V}_{O_2} = (10)\ (A - V_{O_2}\text{ diff})\ (\dot{Q}),$$

where $A - V_{O_2}$ diff is the arteriovenous oxygen difference and $\dot{Q}$ is cardiac output. All comparisons were done using paired sample analysis. Statistical significance was given to p values of 0.05 or less.

After a 15-minute period during which cardiac output, mean aortic pressure and CVP were stable, the endotracheal tube was connected to an air-filled respirometer through a closed CO_2 adsorbing system, and the animal

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[*] All ± values represent one standard error of the mean.

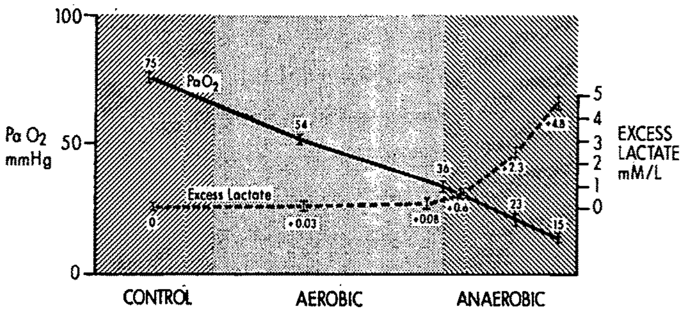

FIG. 1. Effect of Acute Hypoxemia on Arterial Excess Lactate in 10 Dogs. The experimental period was arbitrarily divided into "aerobic" and "anaerobic" periods based upon the appearance of arterial excess lactate. Figures are mean values ± standard error of the mean.

allowed to ventilate unassisted. Blood samples were collected at intervals of 10–15 minutes during the first 20–30 minutes and then every 2.5–5.0 minutes as the hypoxemia became severe.

Results

The experimental phase was arbitrarily divided into two periods (Fig. 1) an aerobic period, during which the hypoxemia was developing but the XL had not accumulated, (mean = 25.5 ± 2.5 min), and an anaerobic period during which XL accumulation occurred (mean = 15.0 ± 1.3 min). Values were then selected from each animal's data at a time representing the control period, half way through the aerobic period, the last normal XL, the first abnormal XL, half way through the anaerobic period, and when possible, just prior to death. As the available O_2 was gradually consumed from the respirometer, Pao_2 fell linearly with time, with a mean rate o descent of 1.8 ± 0.2 mm. Hg/min.

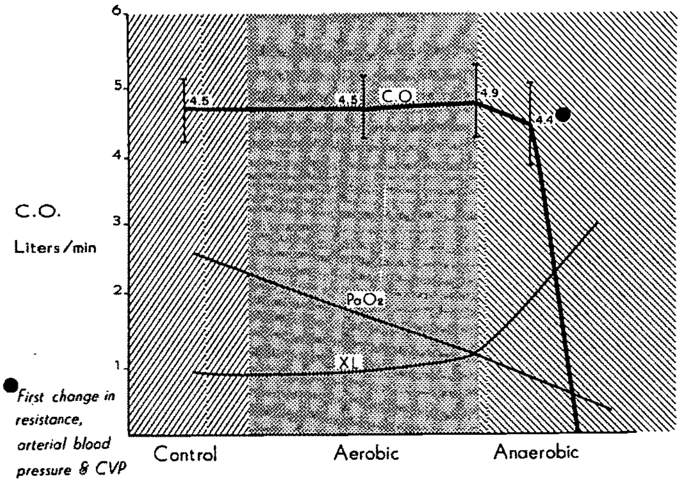

FIG. 2. Effect of Acute Hypoxemia on Cardiac Output. No significant change occurred in cardiac output until the Pao_2 had fallen below 15.3 ± 1.6 mm. Hg. The fall in B.P., Cardiac output and rise in CVP was then precipitous. The early accumulation of lactate at a Pao_2 of 36 mm. Hg represents a response to hypoxemia rather than hypoperfusion.

Excess Lactate: Excess lactate did not accumulat until the Pao_2 had fallen to below 35.7 ± 3.1 mm. Hg (CaO_2 of 12.0 ± 0.9 cc./100 ml., SaO_2 of 74.9 ± 2.4%) XL then accumulated exponentially reaching 4.8 ± 0. mM/L just prior to death.

Cardiac Output: $\dot{Q}$ did not significantly change i either the aerobic or the early part of the anaerobic phas (Fig. 2). During the last half of the anaerobic period however, cardiac output fell precipitously to unmeasurable levels. The fall in $\dot{Q}$ occurred only after the Pao had fallen below 15.3 ± 1.6 mm. Hg (CaO_2 of 7.9 ± 0. cc./100 ml. and SaO_2 of 43.8 ± 3.7%) (Table 1).

CVP, Peripheral Resistance, Arterial B.P.: Right atria pressure did not significantly change until the fall in $\dot{Q}$ There was then a sharp rise in CVP from 0.9 ± 0.7 t 14.1 ± 1.9 cm. H_2O and a rise in mean peripheral resistance from 39.5 ± 6.7 to 60.0 ± 11.0 mm. Hg/L/Min Mean aortic B.P. remained unchanged from control level until immediately preterminally, when it fell precipitously.

$A - Vo_2$ Difference and O_2 Consumption: $A - Vo$ difference did not change significantly from a control o 1.86 ± 0.20 cc./100 ml. during the aerobic period (Fig 3). However, during the anaerobic period, there was sharp drop to 1.09 ± 0.41 cc./100 ml. ($p = 0.06$). Th abruptness of this drop can be appreciated by comparin the value at the end of the aerobic period, 2.28 ± 0.34 and the mid anaerobic value, 1.09 ± 0.41 ($p = 0.05$) $\dot{V}o_2$ did not change significantly during the aerobi period from a control of 4.0 ± 0.5 cc./Kg./Min. Durin the anaerobic phase however, there was a sharp fall t 2.0 ± 0.6 cc./Kg./min. ($p = 0.05$ compared with contro and $p = 0.02$ compared with the $\dot{V}o_2$ at the end of th aerobic period). The fall in $A - \dot{V}o_2$ and Vo_2 occurre prior to the fall in cardiac output and occurred durin the abrupt rise in excess lactate.

Buffer Base Deviation, pH, $Paco_2$: Half way throug the aerobic phase the arterial pH began a rise fror 7.40 ± 0.02 to 7.55 ± 0.02 (Table 1). $Paco_2$ fell progressively from a control of 34.0 ± 1.0 mm. Hg to a low o 16.5 ± 1.2 mm. Hg. Buffer base deviation did not significantly change from a control of −3.3 ± 0.7 mEq/I until the anaerobic phase when a significant fall t −10.6 ± 0.5 mEq/L occurred.

Discussion

This experimental model has demonstrated that chloralose anesthetized dogs, when subjected to progressive acute hypoxemia, do not accumulate XL until the Pao is depressed below 36 ± 3 mm. Hg. This accumulatio has further been shown to occur before cardiac failur

TABLE I

	Control	Aerobic Period		Anaerobic Period		
	Period C	½ Aer.	L.N.X.L.	1st Ab.X.L.	½ An.	P.T.
Arterial O_2 Oxygen Tension mm. Hg	75.6 ±3.7	53.9* ±2.1	35.7* ±3.1	23.1* ±1.8	15.3* ±1.6	
Excess Lactate mM/L	0	−0.025 NS ±0.044	+0.080 NS ±0.047	+0.603* ±0.133	+1.781* ±0.248	+4.830* ±0.759
Cardiac Output L/min.	4.53 ±0.87	4.57 NS ±0.94	4.85 NS ±1.08	4.90 NS ±1.2	4.43 NS ±1.2	Immeas. Low
Lactate mM/L	1.26 ±0.21	1.44 NS ±0.28	1.71 ±0.27*	2.23 ±0.30*	3.45 ±0.38*	6.04 ±0.72*
Pyruvate mM/L	0.175 ±0.029	0.200 NS ±0.032	0.224 ±0.032*	0.223 ±0.030*	0.227 ±0.028*	0.170 NS ±0.015
Central Venous Pressure CmH_2O	−0.9 ±0.7	−1.1 NS ±0.7	−0.7 NS ±0.6	−1.0 NS ±0.6	4.2* ±1.6	14.1* ±1.9
Mean Art. B.P. mm. Hg	144.7 ±5.9	141.5 NS ±6.6	144.5 NS ±7.2	147.0 NS ±9.7	155.0 NS ±10.3	35.0* ±6.2
Mean Systemic Peripheral Resistance mm. Hg/L/Min.	39.5 ±6.7	42.4 NS ±8.9	42.4 NS ±8.5	41.6 NS ±8.2	60.9* ±11.29	?
Arterial-Venous Oxygen Difference ml./100 ml.	1.86 ±0.20	2.25 NS ±0.31	2.28 NS ±0.34	1.41 NS ±0.39	1.09** ±0.41	
O_2 Consumption cc./Kg./min.	4.0 ±0.5	4.6 ±0.6	4.4 NS ±0.6	2.8 NS ±0.6	2.0* ±0.6	
Arterial pH	7.40 ±0.02	7.40 NS ±0.02	7.48* ±0.02	7.51* ±0.03	7.55* ±0.02	7.41*+ ±0.06
Arterial Carbon Dioxide Tension mm. Hg.	34.0 ±0.9	30.5* ±1.8	23.4* ±1.8	20.6* ±2.1	16.5* ±1.2	19.1*+ ±3.1
Buffer Base Deviation mEq/L	−3.34 ±0.69	−5.09 NS ±1.05	−4.76 NS ±0.86	−5.31* ±0.98	−6.06* ±0.9	−10.63* ±0.51
Arterial $SaO_2\%$	95.1 ±0.3	89.5* ±1.3	74.9* ±2.4	63.9* ±3.6	43.8* ±3.7	39.1* ±2.1

Mean values taken from ten dogs at comparable times. C = during control period, ½ Aer. = mid way through the aerobic period, L.N.X.L. = at the time of the last normal excess lactate, F.Ab.X.L. = at the time of the first abnormal excess lactate, ½ an. = mid way through the anaerobic period. P.T. = pre terminal sample. $\bar{x}$ = mean, ± = standard error of the mean. * = statistically significant to the 0.05 level or less when compared with control, N.S. = Not statistically significant when compared with control. + = in some of these animals apnea immediately preceded sampling, ** P = 0.06.

results, and therefore is associated with the hypoxemia itself. The Pa_{O_2} value of 36 ± 3 mm. Hg might be termed the "excess lactate threshold" for these animals subjected to this kind of hypoxemic stress. This value might be expected to vary under different circumstances. For example, different thresholds might have been seen if the rate of fall of Pa_{O_2} had been slower, if cardiac output had been depressed by heavy barbiturate anesthesia, if exercise or fever were causing higher O_2 consumption, or if anemia were present. However, if these variables are kept in mind, some degree of clinical usefulness might be found in this XL threshold.

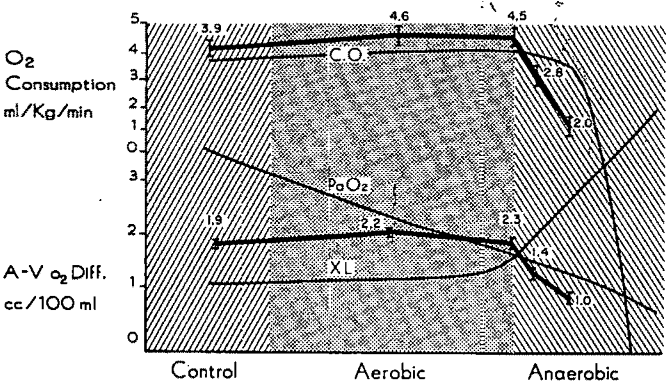

FIG. 3. Effect of Hypoxemia on O_2 Consumption and $A - V_{O_2}$ Difference. The rise in excess lactate, X.L., was accompanied by a reciprocal fall in $A - V_{O_2}$ difference and O_2 consumption. Excess lactate accumulation reflects the developing O_2 debt which occurred below a Pa_{O_3} of 36 mm. Hg.

For example, a Pa_{O_2} of 65–75 mm. Hg is not unusual after thoracic and upper abdominal surgery. Excess lactate accumulation in these patients would not likely be explainable on the basis of hypoxemia alone, and therefore hypoperfusion should be suspected. Similarly, a patient rapidly resuscitated from profound shock, who on the following day develops a Pa_{O_2} of 40–45 mm. Hg and XL accumulation, could be considered to have a hypoxemia severe enough to cause a lacticacidosis without having to hypothesize much, if any, hypoperfusion.

Lactate accumulation is known to be affected by alkalosis. Excess lactate, for example, can accumulate if respiratory alkalosis is prolonged more than one hour, and if the pH is elevated to 7–8 and the Pa_{CO_2} is depressed to 10 mm. Hg. However at Pa_{CO_2} of 15–25 mm.

Hg no significant change in excess lactate will occur during the 1st hour.[6,7] The respiratory alkalosis which occurred during the present experiment was relatively mild (maximum pH of 7.55 ± 0.02), and the XL accumulation occurred within only 20–30 minutes from control. It seems unlikely therefore that this alkalosis significantly affected the excess lactate accumulation in this experiment.

Summary and Conclusions

Because of occurrences of hypoxemia and persistently elevated blood lactate levels following resuscitation from profound shock, an effort was made to determine how far Pa_{O_2} had to be depressed before excess lactate accumulates. Ten dogs were anesthetized with IV chloralose. Endotracheal tubes were connected to an air filled respirometer through a closed, CO_2 adsorbing system, and the dogs allowed to ventilate unassisted. As the available O_2 was consumed, Pa_{O_2} fell linearly with time. Excess lactate did not accumulate until Pa_{O_2} had fallen below 36 ± 3 mm. Hg, and cardiac output did not fall until the Pa_{O_2} had fallen below 15 ± 2 mm. Hg. The sudden rapid excess lactate accumulation was in addition temporally associated with an abrupt fall in O_2 consumption (4.0 ± 0.5 control to 2.0 ± 0.6 cc./Kg./min.) and A − V_{O_2} difference (1.9 ± 0.2 control to 1.1 ± 0.4 cc./100/ml.).

It is concluded that, during acute, progressive hypoxemia, (1) XL accumulation precedes cardiac failure, thereby permitting observation of a "lactate threshold" in hypoxemia; and (2) neither XL accumulation nor cardiac failure occur until the Pa_{O_2} is markedly depressed.

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Hyperglycemia during Cardiopulmonary Bypass

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With the increasing frequency of bypass grafting with cardiopulmonary bypass for occlusive disease of the coronary arteries, an increasing number of patients with diabetes mellitus and coronary atherosclerosis are undergoing operation. A year ago two diabetic patients developed severe hyperglycemia during cardiopulmonary bypass for coronary bypass grafts and subsequently developed fatal hyperosmotic hyperglycemic non-ketotic coma. The correct diagnosis was belatedly made in both patients. Until this time the pump oxygenator had been routinely primed with 12.5 Gm. of 50 per cent glucose because of reports that glucose increased the tolerance of the myocardium to anoxia.[1-5,7,8,10,11] A prospective study of glucose metabolism was accordingly initiated in 20 patients undergoing cardiopulmonary bypass. The findings are described in this report.

Methods

Four diabetic and 16 non-diabetic patients (ages 43–69) were studied. Adult patients were selected at random from the daily operating schedule, studying one patient daily with Class III or Class IV (NYHA) heart disease until a total of 20 had been evaluated.

The four diabetic patients (Group I) were well controlled with daily administration of insulin. In the non-diabetic cases (Group II) preoperative fasting blood sugars or 2 hour post-prandial blood sugars were normal. Twelve of the 20 patients had aorto-coronary bypass procedures, seven had prosthetic valve replacement, and one had removal of a large left atrial thrombus developing after a previous mitral valve replacement.

Anesthesia was induced with thiopental and succinylcholine and subsequently maintained with halothane. Perfusion was at a flow rate of 2.25 L/sq M body surface, temperature 30 to 34° C, using a Pemco roller pump and a Bentley disposable bubble oxygenator. The patients were heparinized with 300 units of heparin/Kg. of body weight. The pump oxygenator was primed with 2000 ml. Ringer's lactate solution and 1000 to 1500 ml. citrated blood. The pH of the citrated blood was adjusted to 7.4 with THAM (tromethamine). In addition, 0.6 Gm. of calcium chloride were given for each 500 ml. of citrated blood, and 1.0 Gm. magnesium sulfate and 10 mEq. of potassium chloride were added. No dextrose was given.

Blood samples were obtained from the patient and the pump oxygenator immediately before bypass, 30 minutes after bypass had begun, and at hourly intervals thereafter. These were analyzed for glucose, sodium, potassium, and osmolality.

Blood glucose levels were measured by the ferrous cyanide autoanalyzer method; osmolality with the Fisk osmometer; sodium and potassium with the flame photometer. Urine samples were collected at the same time as the blood samples were drawn and measured for glucose and acetone. Regular insulin, U-40, was given during operation to the four diabetic patients in Group I and to six of the 16 non-diabetic patients in Group II.

Results

The data from the four diabetic patients in Group I are summarized in Table 1. Blood glucose levels varied between 275 and 520 mg./100 ml. Two to 4+ glycosuria was present, and acetone was present in the urine in one patient. Fifty to 475 units of U-40 regular in-

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TABLE 1. *Glucose Levels and Regular Insulin (U-40) Administration during Cardiopulmonary Bypass in Four Diabetic Patients*

Patient	Operation	Bypass Time (Hr-Min)	Blood Glucose (mg./ 100 ml.)	Urine Sugar/ Volume in cc.	Insulin (Units)
1	A-C Bypass#	3′ 3″	350–385	3+ /1130	55
2	A-C Bypass	2′ 36″	250–305	3+ /1500	50
3	A-C Bypass	4′ 11″	420–520	4+A/ 630	475
4	A-C Bypass	2′ 5″	220–275	2+ / 950	50

KEY: +A = Acetone # = Aorto-coronary bypass

TABLE 3. *Preoperative Serum Sodium and Glycosuria during Cardiopulmonary Bypass in Non-diabetic Patients (Group II)*

Normal Preoperative Serum Sodium		Preoperative Hyponatremia (122-131 mEq/100 ml.)		Total Patients
7 Patients		9 Patients		16
Negative urine sugars	Glycosuria	Negative urine sugars	Glycosuria	
5	2	3	6	16

sulin were given to these four patients during bypass, but in only one did a decrease in blood glucose concentration occur, a 40 mg./100 ml. decrease after 275 units of insulin had been given. Serum sodium concentrations decreased below 131 mEq./L in two of the four patients in this group despite normal sodium concentrations before the operation in both the patient and the pump oxygenator.

In the 16 patients in Group II, blood glucose levels ranged between 180 and 385 mg./100 ml. (Table 2). Ten of the 16 patients developed 1+ to 4+ glycosuria. Twenty to 120 units of U-40 regular insulin were given to six of the 16 patients during bypass. The blood glucose concentration decreased 35 mg./100 ml. in one patient after 10 units of insulin but did not change after administration of a second dose of 30 units. Administration of insulin to the other five patients did not produce any significant change in glucose concentration.

Nine of the patients were hyponatremic preoperatively (122 to 131 mEq./100 ml.) and six of these developed glycosuria during bypass. In addition, two patients with normal preoperative serum sodium concentrations developed hyponatremia and glycosuria during bypass (Table 3). Four of the 16 patients in Group II died in the first 8 days following operation from causes unrelated to hyperglycemia. There were no neurologic injuries.

TABLE 2. *Glucose Levels and Regular U-40 Administration during Cardiopulmonary Bypass in Sixteen Non-diabetic Patients*

Patient	Operation	Bypass Time (Hr-Min)	Blood Glucose (mg./ 100 ml.)	Urine Sugar/ Volume in cc	Insulin (Units)
1	A-C Bypass#	3′30″	285–325	3+/520	40
2	A-C Bypass	4′18″	255–350	4+/1820	60
3	A-C Bypass	3′32″	240–270	1+/490	0
4*	A-C Bypass LV Aneurysm	8′24″	255–300	−/1160	0
5	Double valve	2′28″	275–300	3+/365	20
6	Mitral valve	2′14″	350–380	Tr/175	0
7*	Triple valve	4′19″	200–210	0/300	0
8	A-C Bypass	1′51″	325–345	4+/590	0
9*	Atrial Thrombectomy	2′33″	260–280	0/180	0
10	A-C Bypass	2′ 0″	285–345	1+/270	0
11	Aortic valve	2′ 8″	225–255	2+/915	0
12	Aortic valve	2′35″	180–190	0/180	0
13	Aortic valve	1′54″	360–385	4+A/380	50
14	A-C Bypass LV Aneurysm, Mitral valve	4′10″	250–310	4+A/660	120
15	A-C Bypass	4′14″	260–305	4+/1525	90
16*	Double valve	4′16″	260–285	Tr/1565	0

Key: * = Expired +A = Acetone # = Aorto-Coronary Bypass

In both groups of patients, osmolality values did not rise above 313 mOsm/Kg. of water. This is well below the reported average value of 353 mOsm/Kg. of water found in hyperosmolar hyperglycemic coma.[6]

Within 6 hours after bypass, the blood glucose concentration in both groups of patients decreased to the preoperative levels. Only the diabetic patients required insulin in the postoperative period.

Discussion

The uniform finding in all patients studied, both diabetic and non-diabetic, was the development of hyperglycemia during bypass which was almost totally resistant to the administration of insulin. However, the hyperglycemia promptly subsided within 6 hours after perfusion. These data did not indicate the mechanism for the development of hyperosmotic hyperglycemic non-ketotic coma in the two diabetic patients operated upon earlier. Possibly the addition of glucose to the pump oxygenator may have produced a more severe hyperglycemia in these patients. A greater awareness of the possibility of the development of this complication similarly may have prevented its development in the postoperative course.

The cause of the hyperglycemia, and its resistance to insulin, is uncertain. Tentative explanations have been suggested in other reports, but these are primarily speculative. Measurement of insulin levels during cardiopulmonary bypass with hypothermia has found an inhibition of the normal secretion of insulin in response to infusion of glucose.[7,12] This may represent a hypothermic depression of the response of pancreatic acini to hyperglycemia. The simple process of oxygenation of blood during cardiopulmonary bypass is also associated with a decrease in plasma insulin levels.[5] This may result from changes in composition of plasma proteins, particularly alterations in sulfhydryl group bonding at the blood gas interface.[2]

Data from these studies and reports by others[5,7] indicate that the utilization of insulin is altered during cardiopulmonary bypass, as there is a decreased response to exogenous insulin. Hyponatremia, either from preoperative sodium restriction or hemodilution, may be partly responsible for the decreased sensitivity to insulin, as sodium is required for intracellular transport of glucose, normally initiated by insulin.[1] In this regard it was noteworthy that 10 of 14 of the patients studied with hyponatremia below 131 mEq./L had glycosuria during bypass. Other factors which may inhibit the secretion of insulin include suppression of insulin reactivity with a low cardiac output, and inhibition of insulin reactivity by catecholamines secreted during cardiopulmonary bypass.[9,10]

The frequent occurrence of hyperglycemia during cardiopulmonary bypass indicates that the addition of glucose to the pump oxygenator may be superfluous. Although not demonstrated in these studies, the possibility exists in diabetic patients that such additions of glucose may actually be harmful. The insidious development of fatal hyperosmotic hyperglycemic nonketotic coma in two patients following cardiopulmonary bypass indicates the need for more cautious evaluation of even mildly diabetic patients following operation. It seems probable that instances of fatal neurologic injury from hyperosmotic coma in the past have been erroneously diagnosed as being due to other causes, such as air embolism or vascular occlusion.

Summary

Two fatal cases of neurologic injury with hyperosmotic hyperglycemic non-ketotic coma in mildly diabetic patients following cardiopulmonary bypass prompted a study of insulin and glucose metabolism in 20 patients undergoing cardiopulmonary bypass for different lesions. Four diabetic and 16 non-diabetic patients were studied. Some degree of hyperglycemia developed in almost all patients studied during bypass. In the diabetic patients the blood glucose levels ranged from 275 to 520 mg./100 ml., while the glucose levels in the 16 non-diabetic patients ranged from 180 to 385 mg./100 ml. The hyperglycemia was almost totally resistant to administration of regular insulin during bypass, up to 475 units. However, following bypass the hyperglycemia subsided within about 6 hours. No adverse complications were detected. The cause of the hyperglycemia and its resistance to exogenous insulin is uncertain. Serum osmolality values remained below 313 mOsm/Kg. There was some glycosuria and mild hyponatremia.

Although the mechanism of hyperosmotic coma was not detected in these studies, the uniform occurrence of hyperglycemia during cardiopulmonary bypass indicates that further addition of glucose during perfusion is superfluous and may possibly be harmful.

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Calciphylaxis.

Etiology of Progressive Vascular Calcification and Gangrene

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PROGRESSIVE generalized vascular calcification, severe enough to produce arterial insufficiency and ischemic tissue necrosis after successful renal homotransplantation, is rare. When this degree of calcification has been reported, it has been associated with secondary or tertiary hyperparathyroidism. The calcifications usually regress almost completely within 2 months of transplantation.[12] In the remaining patients, subtotal parathyroidectomy has been followed by regression of vascular calcification and healing of ischemic ulcers.[5,9] The case reported here is unique due to the generalized vascular calcification which developed and progressed in the absence of hypercalcemia. Subtotal parathyroidectomy, despite producing hypocalcemia, failed to arrest progression of the vascular calcifications and tissue necrosis. The vascular lesions resulted in severe ischemia and peripheral gangrene which finally caused amputation of three extremities.

Calciphylaxis has been proposed as a possible mechanism in the pathogenesis of soft tissue and vascular calcification in chronic renal disease.[5,6] In this process, as defined by Selye,[10,11] local or generalized calcinosis followed by inflammation and sclerosis may be produced by prior tissue sensitization by a systemic calcifying factor such as parathyroid hormone, vitamin D, or hypercalcemia followed by treatment with another agent at some later critical period. This need not be at a time when the plasma calcium level is high since the challenging agents may act as a mordant to prepare the already sensitized tissues for the deposition of calcium. It is possible, as proposed by Massry,[5] that prednisone acting as a challenger, may lead to calciphylaxis in tissues previously sensitized by high levels of endogenous parathyroid hormone. Corticosteroids have been shown to aggravate or produce calciphylaxis under some circumstances in experimental animals.[10]

Case Report

A 23-year-old woman was first seen in December 1966, because of progressive renal failure secondary to diffuse exudative glomerulonephritis. Blood urea nitrogen was 170 mg./100 ml., serum calcium 8.3 mg./100 ml., *ionized calcium 4.5 mg./100 ml.,* and phosphorus 11.7 mg./100 ml. Bone survey x-rays were normal with no vascular or soft tissue calcifications. Bone biopsy showed osteosclerosis. A Scribner shunt was placed in the right arm to facilitate chronic hemodialysis. Three months later a cadaveric renal homotransplantation was performed; however, renal function was never sufficient to permit cessation of dialysis, so the graft was removed 6 weeks later.

Over the next 12 months she was treated by hemodialysis using both the twin-coil and the parallel flow dialyzers. Standard dialysate mixed with nondeionized tap water was used two to three times per week for a total of 12 to 20 hours per week. Predialysis serum calcium levels averaged 9.6 mg./100 ml., serum phosphorus 9.2 mg./100 ml., with a calcium phosphorus product of 88 and serum alkaline phosphatase 12.7 Shinowara-Jones units (normal range 2–9). Post dialysis serum calciums averaged 12.2

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ng./100 ml., serum phosphorus 5.1 mg./100 ml., with a calcium phosphorus product of 63 (Table 1). Slight osteoporosis of the umbar spine was noted months after admission, and for the first ime soft tissue calcifications adjacent to the lateral humeral epicondyle were seen.

A second transplant was performed 12 months later. Postoperatively her endogenous creatine clearance stabilized at 30 ml./min., at which time her mean calcium phosphorus product was 54. Drug therapy included azothiaprine and prednisone. Skeltetal x-rays at this time revealed bursal calcification about the head of the left humerus, with tapering of the lateral aspect of the eft clavicle, suggestive of subperiosteal reabsorption. Repeat x-rays 18 months after the initial study revealed extensive metastatic calcification in both elbows, wrists, and hands. Dental films showed alveolar reabsorption with slight crown erosion. Painful ischemic ulcers of the right lateral gluteal region and thigh developed and gradually extended in the ensuing months despite intensive local therapy.

Six months after transplant, the patient was admitted with ischemic rest pain in the ring and middle fingers of the right hand. Examination of the right hand revealed pallor, pain, and hypothermia with no pulses felt distal to the brachial. The circulation improved with intravenous heparin and low molecular weight dextran therapy. X-rays of the right hand and forearm obtained at this time showed extensive small and large vessel vascular arterial calcification as well as widespread soft tissue calcifications (Fig. 1). Two months later she was rehospitalized because of progressive ischemia of both hands, as well as progression of the lesions on the right thigh. X-rays at this time showed widespread vascular calcification and diffuse soft tissue calcifications including calcific bursitis of both shoulders. Right brachial angiography revealed occlusion of both radial and ulnar arteries with multiple calcified vessels in the hand which did not visualize on delayed serial views.

Pertinent blood chemistries following transplantation included a mean serum calcium of 10.0 mg./100 ml. (range: 9.0–11.7), mean serum phosphorus 5.2 mg./100 ml. (range: 3.8–5.8), and calcium phosphorus products ranging from 49–57 (Table 2). Endogenous creatinine clearance remained stable at 25–30 ml. per minute. On the basis of the clinical, radiological, and biochemical findings subtotal parathyroidectomy was performed in an attempt to control the morbid calcinosis. Also, cervicodorsal sympathectomy was done hoping to improve digital blood flow. The three and one-half parathyroid glands removed showed minimal hyperplasia. Postoperatively, serum calcium decreased to 8.3 mg./100

TABLE 1. *Pretransplant Clinical Course*

Date	Initial Data 12/66	Hemodialysis 12/66–1/68	
		Pre-Dialysis	Post-Dialysis
Ischemic Symptoms	None	—	None
X-ray Findings	Normal	—	Normal
CCr	5	5	—
Serum Calcium: Mean (mg./100 ml.)	8.3	9.6	12.2
(Range)	—	(7.7–12.1)	(11.4–14.3)
Ser. Phosphorus: Mean (mg./100 ml.)	11.7	9.2	5.1
(Range)	—	(4.3–14.4)	(3.9–7.0)
Ionized Calcium (mg./100 ml.)	4.5	6.0	7.9
Alkaline Phosphatase*	—	12.7	—
Ca × P	97.1	87.7	63.0

*Shinowara-Jones Units

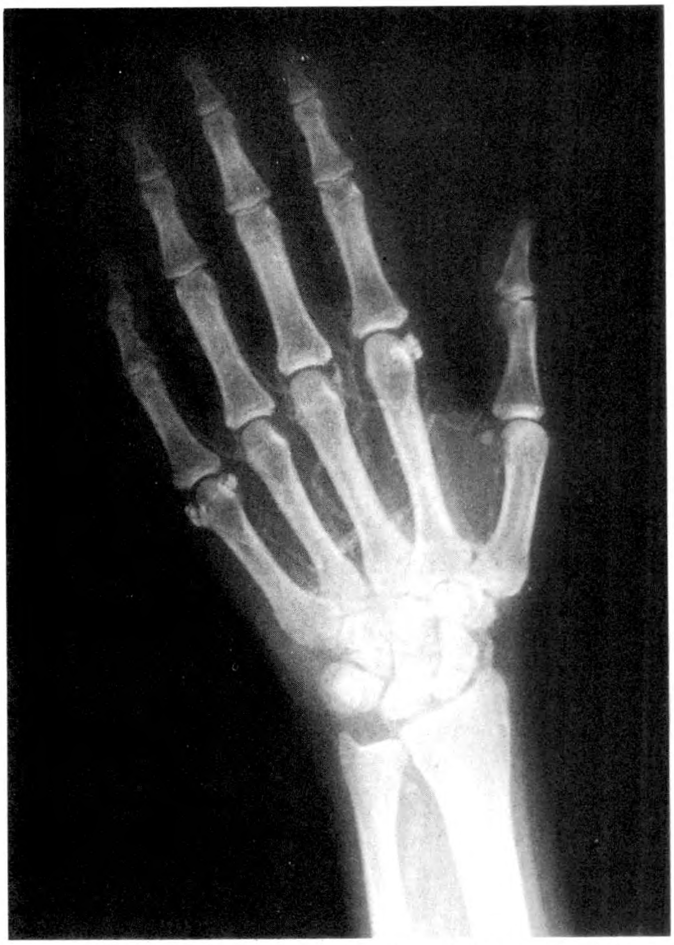

FIG. 1-a. Diffuse soft tissue and vascular calcification of small and medium sized arteries of hand with sever ischemia secondary to fibrous obliteration of lumen of vessels.

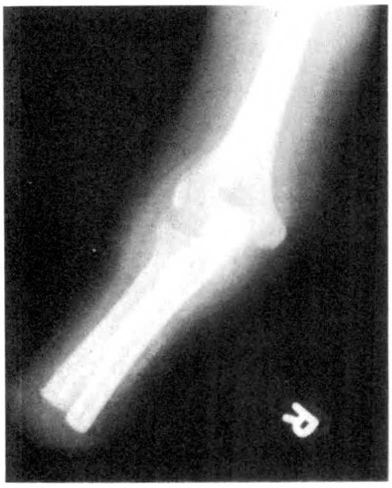

FIG. 1-b. Amputation stump and upper arm show similar calcifications.

TABLE 2. *Post-transplant Clinical Course*

	Pre-Parathyroidectomy	Post-Parathyroidectomy	
Date	12/67–10/69	10/69–5/70 Period I	6/70–9/70 Period II
Ischemic Symptoms	6/68—Ulcerations Buttock & Thigh 6/69—Ischemic R. Hand	10/69—Amp. R. Hand 4/70—Amp. L. Hand	9/70—Amp. L. Leg 9/70—Death
X-ray Findings	4/68—Bursal Calcification 6/68—Widespread Soft Tissue Calcification 6/69—Progressive Arterial & Soft Tissue Calcification 9/69—Occlusion R. Radial & Ulnar Arteries	3/70—Extensive Arterial Calcification	
CCr	25–30	22.0	7.6
Serum Calcium: Mean (mg/100 ml)	10.0	8.8	8.2
(Range)	(9.0–11.7)	(7.3–10.8)	(8.1–8.4)
Ser. Phosphorus: Mean (mg/100 ml)	5.2	5.5	5.8
(Range)	(3.8–5.8)	(4.2–7.6)	(5.6–6.5)
Ionized Calcium (mg/100 ml)	4.6	4.3	4.3
Alkaline Phosphatase*	—	4.2	5.9
Ca × P	49–57	48.5	47.0

* Shinowara — Jones Units

ml., serum phosphorus 5.6 mg./100 ml., and alkaline phosphatase 3.4 units with a calcium phosphorus product of 48. *Calculated ionized calcium levels were essentially unchanged.* Relentless progression of gangrene of the right hand required mid forearm amputation 2 weeks after the parathyroidectomy. There was extensive medial calcification with marked intimal and subintimal thickening of the radial and ulnar arteries, with fibrous obliteration of the lumen. She then developed gangrene of the index and middle fingers of the left hand requiring amputation of these fingers 1 month later (Fig. 2). X-rays at this time showed almost complete calcific visualization of the medium and small sized arteries of the extremities, trunk, and chest. She next developed arterial insufficiency of the left foot which progressed, and below the knee amputation of the left leg became necessary. Following this, she went downhill and died 3 years after the onset of renal failure and 21 months post-transplantation.

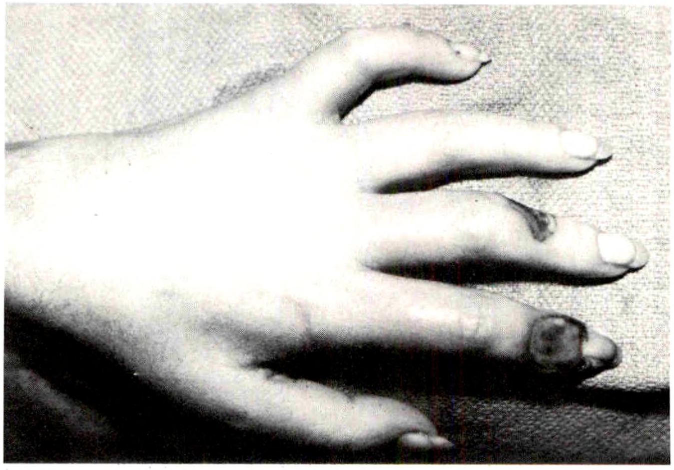

FIG. 2. Gangenous areas of index and middle fingers of left hand which eventually required digital amputation.

Autopsy revealed generalized medical calcification with fibrous obliteration of the lumen of all vessels studied, extensive interstitial and vascular calcifications within the myocardium, and marked pulmonary interstitial calcifications (Fig. 3.) The patient's own kidneys showed diffuse medial calcification of the muscular arteries with widespread glomerular calcification (Fig. 4). Abnormal calcifications were not present in the transplanted kidney.

Discussion

Metastatic soft tissue calcification in uremia is usually attributed to chronic elevation of the plasma calcium-phosphorus product. When this value is more than 60 plasma solubility is exceeded and precipitation of calcium salts occurs. Local, as in the kidney, and systemic, as after hemodialysis, increases in pH may predispose to this precipitation.[6] In our patient, metastatic calcification became apparent after renal function had been restored and when the calcium phosphorus product was minimally elevated.

Vascular calcifications are frequently seen in patients with chronic renal failure. Radiologic evidence of vascular calcification was reported by Katz[3] in 38 of 195 patients with chronic renal failure, and by Friedman[2] in eight of 20 patients treated with chronic hemodialysis. Pendras found vascular calcification in 20% of patients without evidence of hyperparathyroidism on chronic hemodialysis; this figure rose to 58% in patients who developed secondary hyperparathyroidism, and to 75% in those with autonomous or tertiary hyperparathyroid-m.[1,4,7] Despite the frequency of vascular calcification, rterial insufficiency and tissue necrosis associated with ronic renal failure or chronic hemodialysis has been resent in only a few isolated cases.[3,5,8,9]

Arterial calification in uremia is usually localized to e tunica media, resulting in a pipestem pattern of alcification, such as is seen in Monckebergs' arterio- lerosis.[6] Intimal calcification, as seen in atheromatous laques, is rare in uremia, thus explaining the usual ck is ischemia in spite of marked roentgenographic bnormalities. Occasionally, however, fibrous oblitera- on of the lumen develops, perhaps in response to the edial calcification; thereby producing ischemia as in ur patient.

Progression of vascular calcification resulting in tissue ecrosis after successful renal transplantation is ex- remely rare with only two cases reported.[5,9] In both, ignificant hypercalcemia was present following renal omotransplantation. In one, subtotal parathyroidectomy esulted in progressive regression of the vascular cal- ifications over a period of 1 year.[9] The second patient ied of sepsis 39 days after subtotal parathyroidectomy. ostoperatively, the serum calcium returned to the ormal range without signs of clinical improvement.[9]

In contrast, our patient did not exhibit hypercalcemia ollowing successful renal transplantation. Nevertheless, ascular calcification, which had not been detectable hile she was on dialysis, appeared and progressed o cause widespread arterial insufficiency and peripheral angrene. Subtotal parathyroidectomy failed to halt the rogression of her vascular disease during the remaining 1½ months of life. Amputations were required of three xtremities. During this entire period, serum calcium emained in the low normal or hypocalcemic range Table 1).

Microscopic vascular calcifications which occur prior o transplantation may have predisposed to calciphylaxis nd the addition of prednisone therapy post-trans- lantation precipitated the calcinosis, even though hyper- alcemia no longer existed. Calciphylaxis, once underway, ay not be reversible by restoration of renal func- ion or by parathyroidectomy. If so, parathyroidectomy ay not be advisable in similar cases of severe vascular nd soft tissue calcification without hypercalcemia in he post-transplant patient.

Summary

A patient is described in whom progressive vascular alcification and severe peripheral ischemia developed fter apparent successful renal homotransplantation. he progressive ischemia resulted in eventual gangrene, hich required amputation of three extremities, finally nded in death. Subtotal parathyroidectomy with pro-

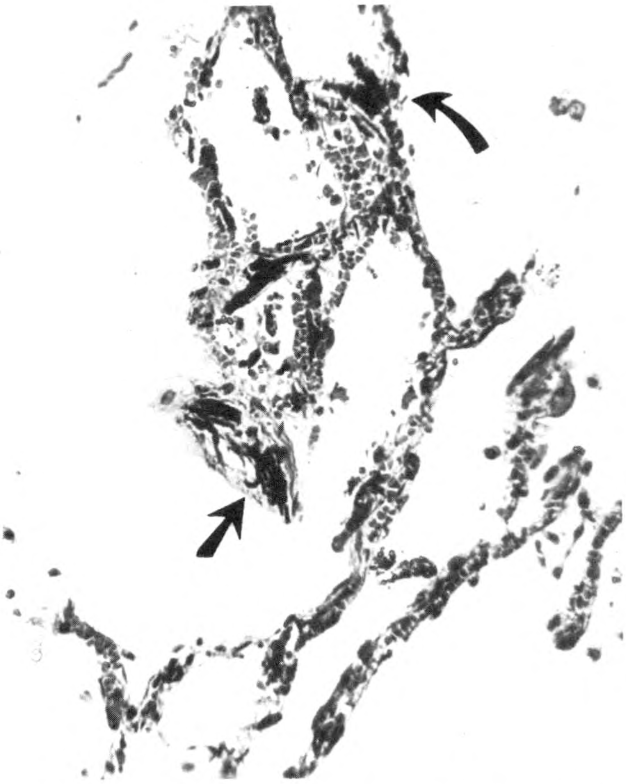

FIG. 3. Extensive pulmonary interstitial calcifications found at autopsy. Hematoxylin and eosin stain. Magnification 250×.

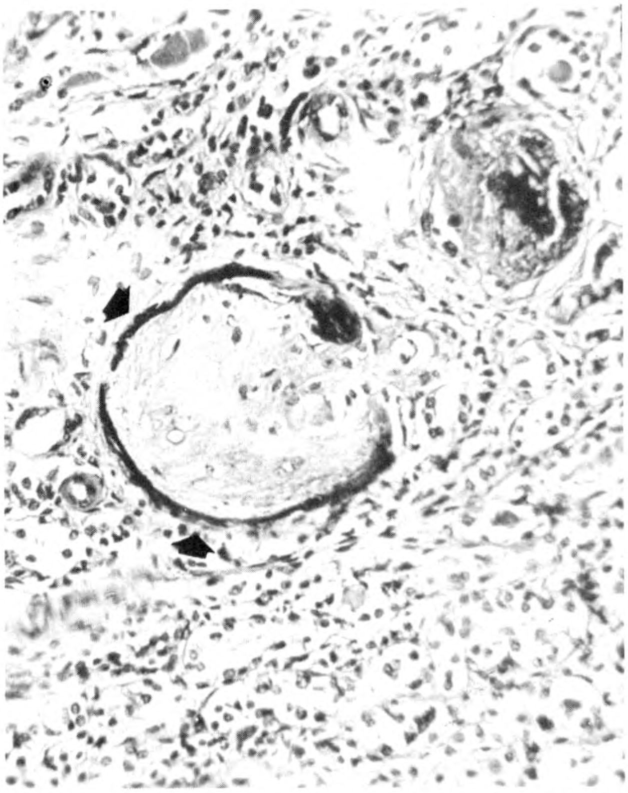

FIG. 4. Extensive calcification of glomeruli of patient's own kidney. Hematoxylin and eosin stain. Magnification 250×.

duction of hypocalcemia failed to produce regression or cessation of the progressive vascular and soft tissue calcifications. Calciphylaxis is proposed as a possible mechanism for this previously unreported sequence of events.

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Effect of Hemorrhagic Shock on Pulmonary Interstitial Sodium Distribution in the Primate Lung

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IN A PREVIOUS STUDY, the effect of hemorrhagic shock on primate lung structure was investigated.[12] Using special technics, light microscopy demonstrated diffuse interstitial edema following 2 hours of profound hemorrhagic hypotension. Electron microscopy revealed that the edema was primarily located in the interstitial space of the alveolar capillary membrane. The ultrastructural findings included increased distance between individual collagen fibers and in some cases distortion of the collagen fibers. Both endothelial and epithelial layers appeared undamaged. In the presence of intact lining layers and low capillary hydrostatic pressure, the development of interstitial edema is puzzling. Among a number of possible explanations, one relates to the possible changes in collagen sodium concentration during prolonged hypoperfusion. Hemorrhagic shock is known to be associated with the development of metabolic acidosis, primarily as a result of lactic acid accumulation. A reduction in pH has been shown to heighten the affinity of collagen for sodium and water.[6] Thus it is possible that the acidosis existing during hemorrhagic shock may lead to the accumulation of sodium and water in areas occupied by the collagen fibers of the alveolar capillary membrane.

To test the hypothesis that increased amounts of sodium accumulate in areas of the pulmonary interstitium occupied by collagen fibers following hemorrhagic shock, it is necessary to be able to identify sodium distribution. This can be accurately accomplished by ultrastructural histochemical technics. Such a technic for sodium localization was first proposed by Komnick and co-workers[10] in 1962. The principle of this method involves the fixation of a given tissue with an aqueous solution of unbuffered pyroantimonate. This solution possesses two important characteristics: 1) the pyroantimonate ion has a great affinity for sodium, and 2) the resulting complex, sodium pyroantimonate, is insoluble and appears as electron opaque particles. Recently Das Gupta *et al.*[5] have modified this technic for use in primate lung tissues. The method utilizes *in vivo* dual simultaneous fixation through both the vascular and endobronchial systems to insure even fixation and minimize distortion during processing.

The object of this report is to describe the distribution of sodium pyroantimonate precipitates in the primate lung interstitium in the control state and following profound hemorrhagic shock.

Method

Eight adult baboons (Papio doguera) weighing between 9 and 18 Kg. were the test animals. Prior to study, each animal was tranquilized with 0.8 mg./Kg. of Serylan (1 phenylcyclohex—piperidine hydrochloride), a primate tranquilizer. An endotracheal tube was then inserted. Under local anesthesia siliconized plastic catheters were placed in the aorta and inferior vena cava via the femoral vessels. The arterial catheter was used for bleeding and for measuring arterial pressure. The venous catheter was used to measure venous pressure. The animals were then placed in the prone position and the anterior chest wall was protected by axillary pads.

Hemorrhage. After a base line period of approxi-

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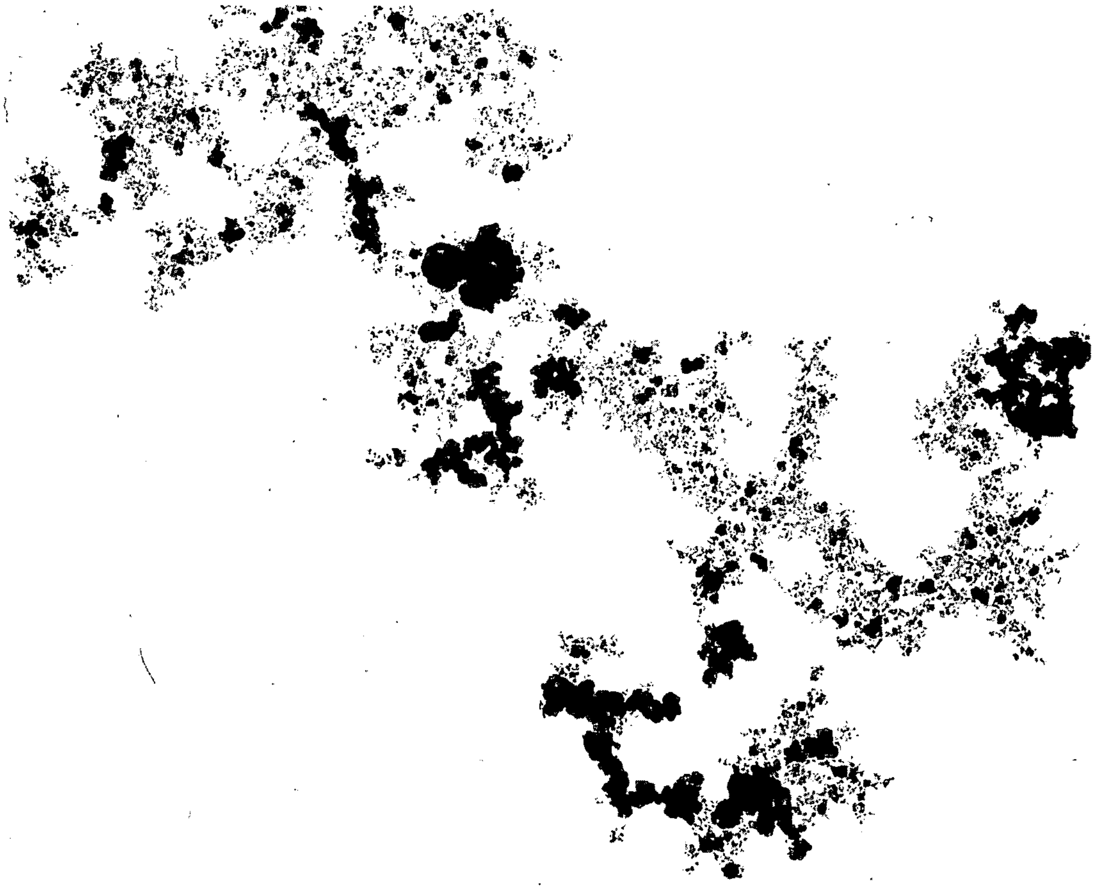


FIG. 1. Sodium pyroantimonate precipitate. This was obtained by adding 9 cc. of perfusing fluid to 9 cc. of 0.9% NaCl solution (× 35,060).

mately 3 hours, animals were bled into a sterile plastic bag containing 67.5 cc. of acid citrate dextrose solution. The arterial pressure was reduced over a period of 15 minutes to 60 mm. Hg, and maintained at this level for 1 hour. It was then reduced to 40 mm. Hg and maintained for a second hour.

Technic of In Vivo Dual Lung Fixation. At the conclusion of the 2-hour shock period, the animal was placed in the supine position and the extremities were restrained. A small dose of pentobarbital was given intravenously. The thoracic cavity was entered through a midline sternal splitting incision. A pursestring suture was then placed in the main trunk of the pulmonary artery and a siliconized plastic catheter was threaded into the left pulmonary artery. A similar catheter was threaded through the endotracheal tube to the left main bronchus. By cross-clamping the right lung hilum, the left lung was isolated. A dual method of perfusion fixation through both the vascular and endobronchial systems was then initiated. The perfusion pressure in the arterial system was maintained at a steady 40 cm. of water. After a few minutes of perfusion through the vascular bed, the ascending aorta was clamped, thus reducing the quantity of the perfusate needed. Approximately 500 to 700 cc. of the perfusate was given in 30 minutes. Another 20 to 40 ml. of the perfusate (the volume of fluid to fill the main stem bronchus and its branches) was manually instilled into the bronchus through the catheter. The catheter was then removed and the endotracheal tube clamped. At the end of 30 minutes of this dual fixation the lung was firm in consistency and resembled liver in gross appearance. The lung was then removed and tissue samples were taken from different areas. The baboon was then sacrificed.

The perfusate, an aqueous solution of potassium pyroantimonate (K. and K. Laboratories, Inc., Plainview, N. J.), was prepared with the aid of heat and allowed to cool. In 40 ml. of this solution, 0.5 Gm. of osmium tetroxide was dissolved in 0.5 to 1.0 ml. of 0.1 N hydrochloric acid and added to the mixture. The pH of the resulting solution was adjusted to 7.6 with 0.01 acetic acid and the volume was made up to 50 ml. For this type of investigation, in which large quantities of the mixture are required, the proportion of the constituents is increased to make up a total of 1,000 cc. of the perfusing mixture of pyroantimonate and osmium. This unbuffered mixture must be made up on the day of perfusion.

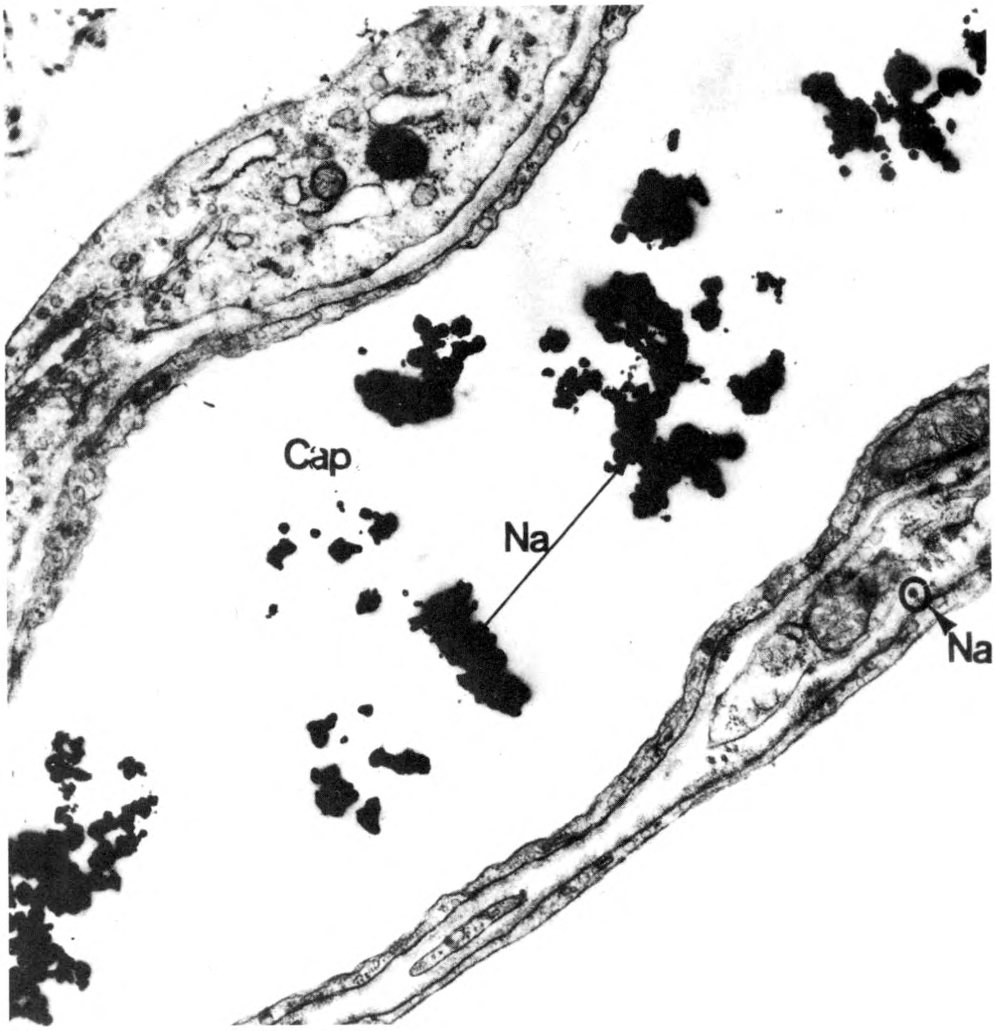


FIG. 2a. The sodium pyroantimonate precipitate in a pulmonary capillary. Note the alveolar capillary membrane in either side of the capillary lumen. Sodium pyroantimony precipitate deposits (Na) can be seen distributed in the interstitial space (× 25,200).

Following perfusion, slices of lung tissues were further fixed by immersion in the same perfusate for 2 hours at 4°C. Fixed tissues were quickly dehydrated in acetone and embedded in Araldite. The specificity of the chemical reaction was ascertained by adding the unbuffered pyroantimony solution to 0.9% sodium chloride solution. The resulting precipitate, sodium pyroantimonate, was sprayed in a grid and viewed.

Technic of Electron Microscopy. Ultrathin sections were cut and mounted on a copper grid. These were stained on the grid with an alcohol solution of uranylacetate and viewed in a RCA EMU 4 microscope.

Results

The results of mixing equal volumes of isotonic saline with aqueous potassium pyroantimonate are shown in Figure 1. The resultant complex, sodium pyroantimonate, is seen as electron opaque substances. A similar pattern will be seen in tissues fixed with this solution.

The mechanism of movement of sodium from the plasma to the pulmonary interstitium is not known. Theoretically, it might pass through intercellular clefts or it might be carried across the endothelial layer by way of pinocytotic vesicles. In Figure 2a, sodium precipitates can be seen within the capillary lumen and also within the interstitial zone. In Figure 2b, sodium is found adjacent to both an intercellular junction as well as a pinocytotic vesicle. However, in Figure 2c, sodium precipitates can be located within pinocytotic vesicles. While this same relationship seen in Figure 2c was frequently observed in other sections, sodium precipitates were never seen within intercellular junctions. This suggests a role for pinocytosis in sodium transport in the lung.

In Figure 3a, a low-power view of the normal alveolar capillary membrane, the discrete distribution of the sodium precipitates can be seen. It should be noted that the major sodium concentration is in proximity to collagen fibers. At higher magnification, as demonstrated in Figure 3b, a large fraction of the sodium is actually within individual fibers.

The effects of 2 hours of hemorrhagic shock on sodium distribution are shown in Figures 4a and 4b. In Figure

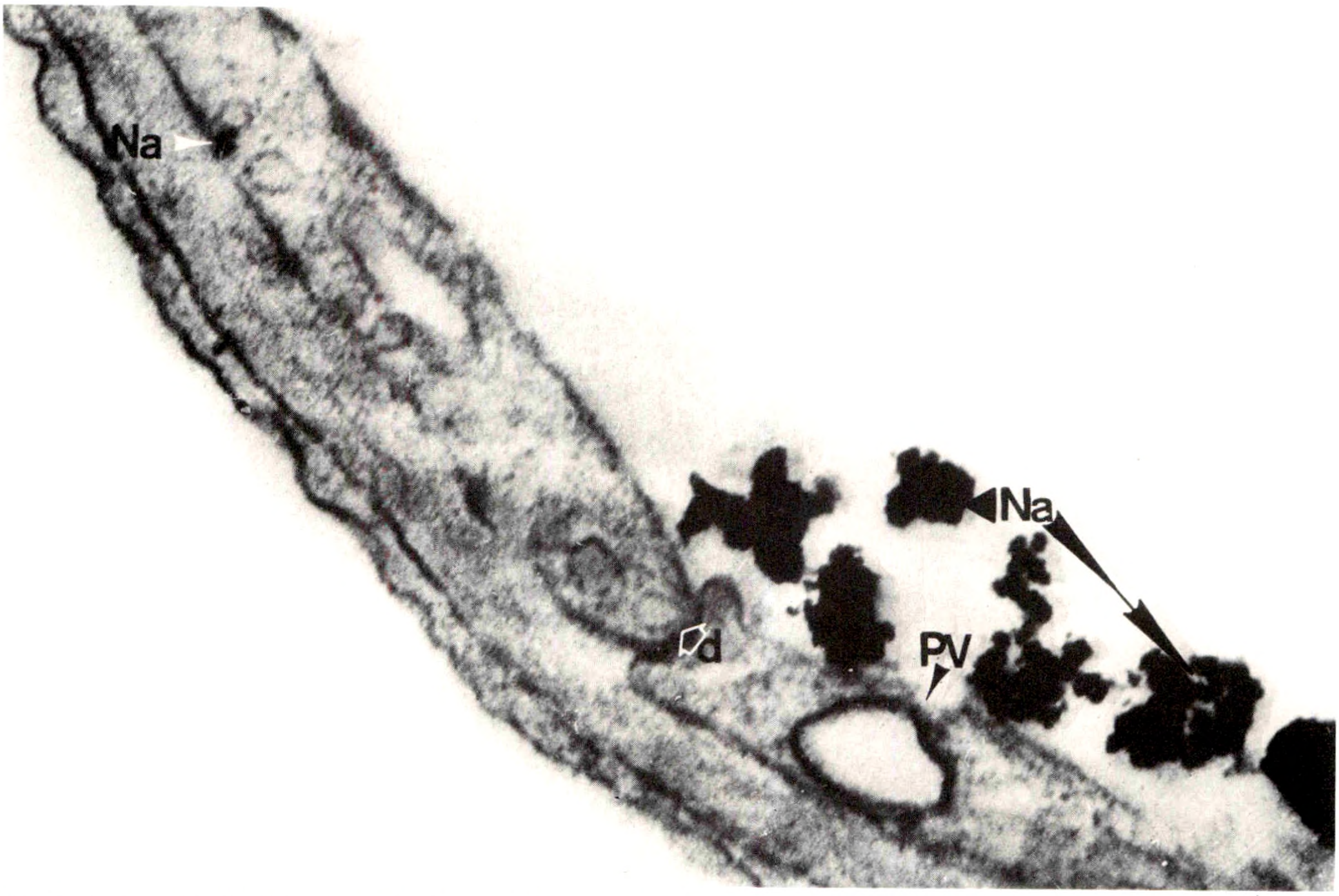


FIG. 2b. The endothelial lining of a pulmonary capillary under high power, showing the tight junction (d) and the surrounding sodium pyroantimony precipitate (Na). Note that no precipitate is passing through this desmosomal contact. A cluster of precipitates are adjacent to a pinocytotic vesicle (× 34,800).

4a, a low-power view of the alveolar capillary membrane, profound differences can be seen as compared to the control state (Fig. 3a). These differences include the appearance of large areas of interstitial, intensely stained smudging, indicating sodium-rich edema fluid; dispersion of individual collagen fibers, again suggesting edema; and intensely-stained individual collagen fibers, indicating increased take-up of sodium. Figure 4b shows in greater detail the smudging, the dispersion of individual collagen fibers, and the intense staining of the fibers.

The mechanism of sodium endothelial transport in the shock state is similar to that in the control state. Figure 5 shows that sodium pyroantimonate precipitates are discretely localized within the pinocytotic vesicles. None were seen within intercellular junctions.

Discussion

To our knowledge, this is the first histochemical study of sodium distribution in the lung. Several points described in the results section deserve comment. First, the movement of small and large molecules across intact membranes has been studied by several investigators.[4] Their results indicate that small molecules, such a sodium ions, are more likely to move across the membranes between intercellular junctions than by way of pinocytosis. However, we observed numerous instances in which sodium was visualized within pulmonary endothelial vesicles in both the control and shock state; and conversely we never observed sodium within an intercellular junction. In addition, we found no evidence of endothelial damage or disruption following shock. Another point in favor of pinocytosis as a bulk carrier of sodium is the observation made by us[12] in a previous report that the number of pinocytotic vesicles substantially increases during shock. Thus, one of the factors determining the amount of sodium deposited in the interstitium may be the rate of pinocytotic activity in the endothelial layer.

A second point of interest is the pattern of sodium distribution once it reaches the interstitial zone. Under normal circumstances sodium is distributed around groups of collagen fibers and within individual fibers. After a period of hemorrhagic hypotension, the concentration of sodium pyroantimonate in these same areas is

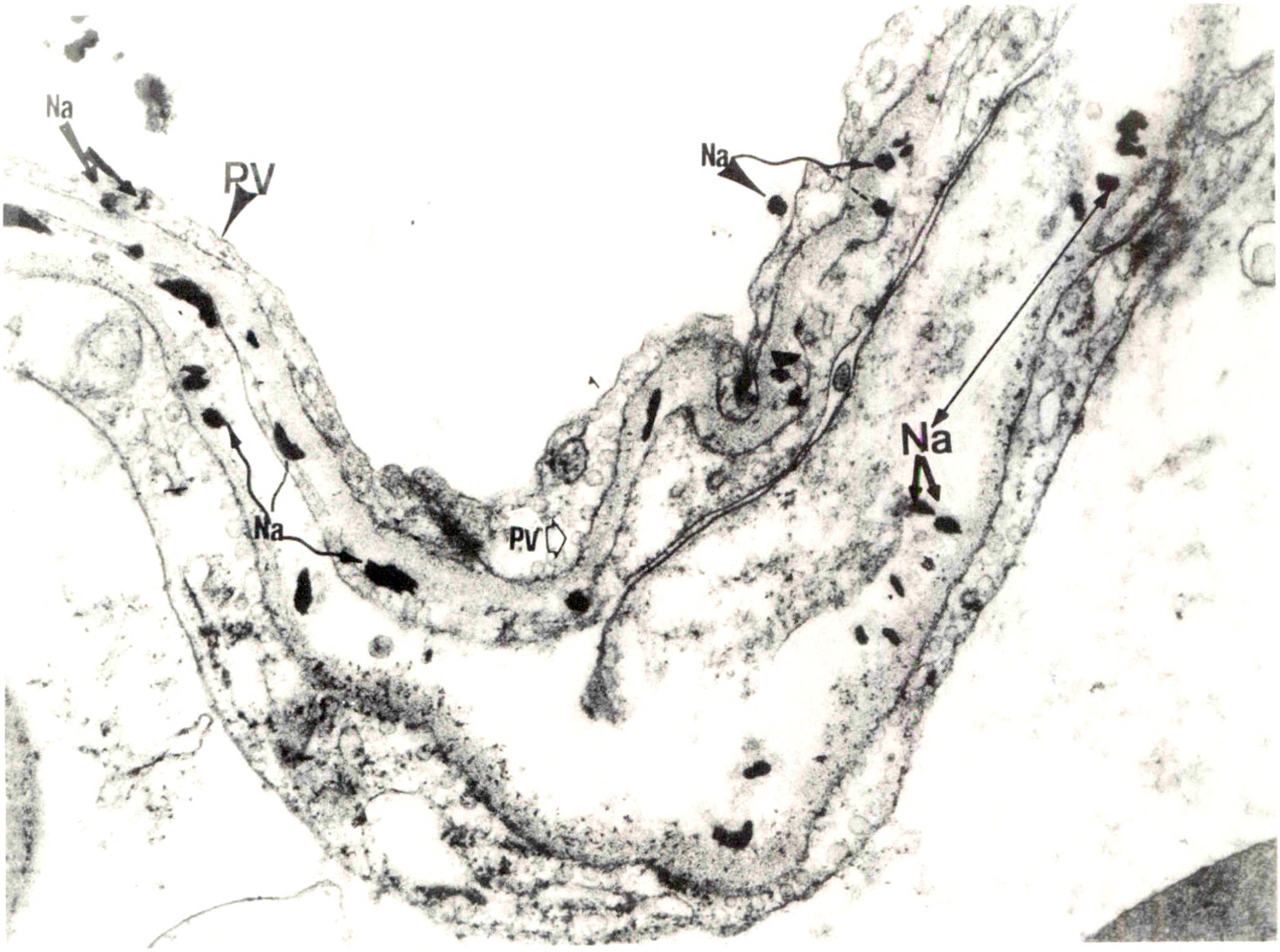


FIG. 2c. The distribution of sodium pyroantimony precipitate (Na) within the pinocytotic vesicles (PV) and the interstitial space in a control lung. Note the progression of the sodium pyroantimony precipitates from the pinocytotic vesicles to the collagen fibers (CO) (× 42,000).

substantially increased and pools of sodium-rich edema fluid develop within the interstitium. These observations suggest that collagen possesses a basal affinity for sodium and furthermore this affinity is heightened after a period of hemorrhagic hypotension. In addition, the increased local concentration of interstitial sodium should favor the movement of plasma water into the interstitial zone. From these observations a conceptual rendition of sodium transport and distribution in control lung tissue and in lung tissue examined after 2 hours of hemorrhagic shock is shown in Figures 6 and 7.

Since the pyroantimony technic was originally described in 1962, the specificity and sensitivity of this method of sodium marking has been tested by a number of investigators. The most serious problem was identified by Bulgar,[2] who showed in *in vitro* studies that precipitates could be formed with other cations, including potassium, magnesium, and calcium. Since all three cations are found in relatively high concentrations within cell cytoplasm, interpretations of intracellular precipitates must be made with caution.

On the other hand, extracellular precipitates appear to be primarily sodium pyroantimonate. The evidence for this is as follows: 1) Pyroantimonate is approximately 10 times more sensitive for sodium than the other cations. 2) While other cations are present in low concentrations, sodium is the principle extracellular cation. 3) If tissues are harvested in a solution high in sodium content prior to fixation with pyroantimonate, there is a qualitative increase in interstitial precipitates.[2] 4) If specimens of gluteraldehyde-fixed tissue are kept in a sodium-free phosphate buffer solution for 5 days prior to pyroantimonate treatment, only negligible amounts of precipitates can be seen.[2] 5) Electron microscope autoradiography of kidney tissue has shown that the precipitates contain sodium.[14] 6) In tissues fixed with pyroantimonate, radioactive sodium ions show a slower efflux than that seen in controls.[17] For these reasons, Torack and

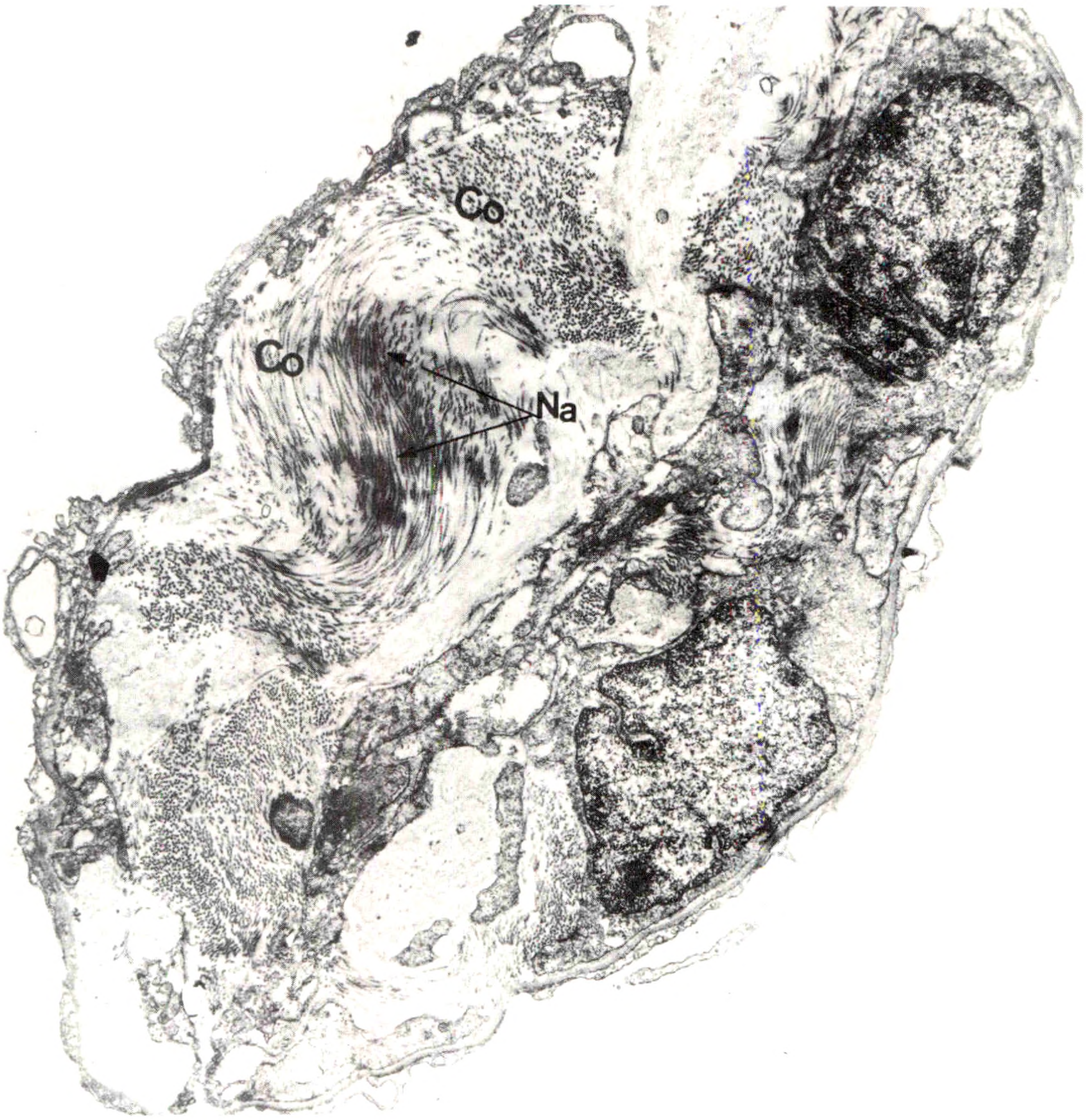
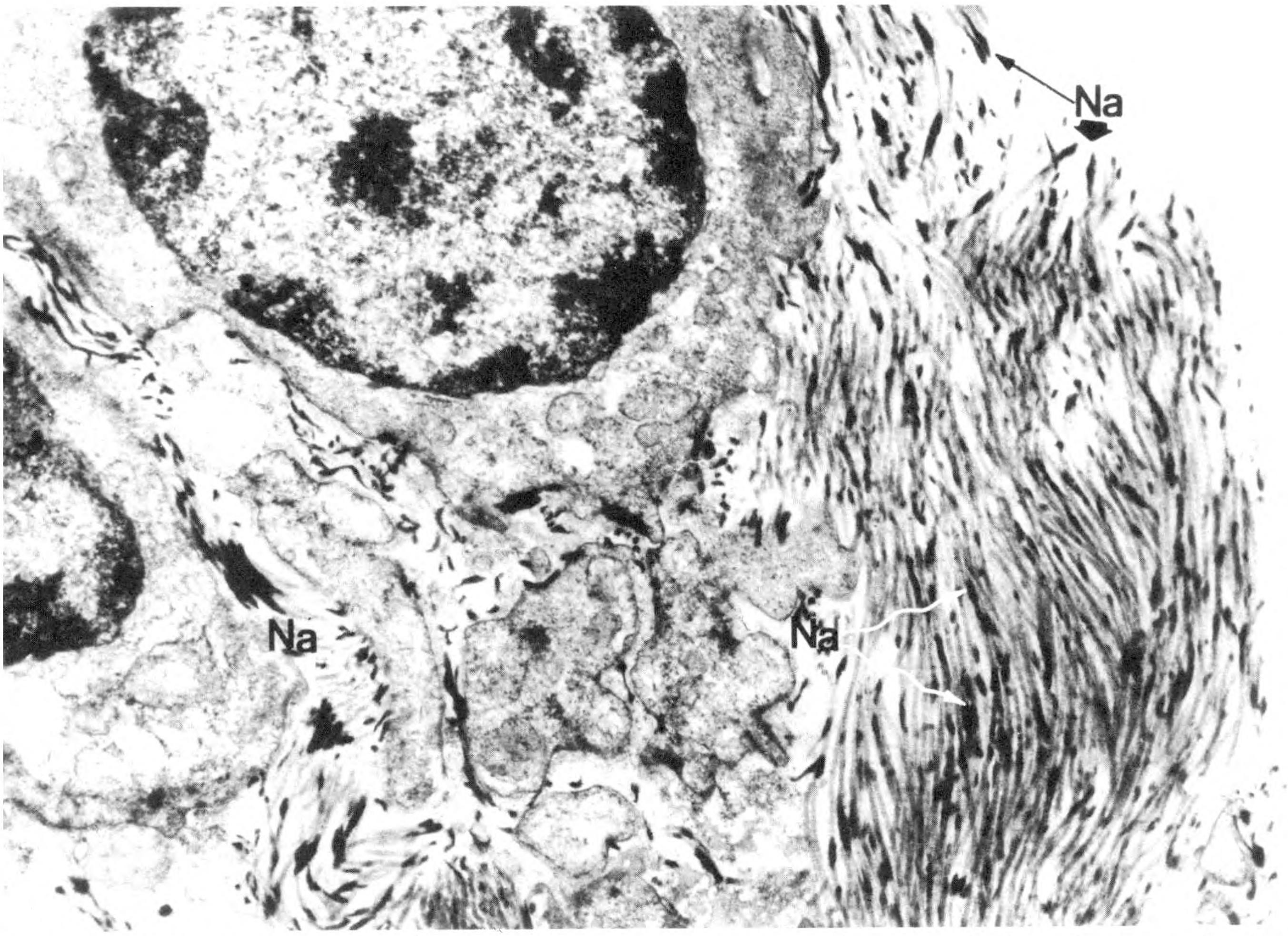


FIG. 3a. This is a low-power view of the normal alveolar capillary membrane. The discrete distribution of sodium (Na) can be seen in and around collagen fibers (× 9,900).

LaValle[15] recently concluded that extracellular localization of sodium ion by this technic should be considered to be a valid representation of this cation.

In vivo fixation is an important aspect of this technic for several reasons. It is self-evident that fixation in the living state should minimize the immediate changes associated with hypoxic cellular injury and death. Another aspect relates to the postmortem movement of sodium ions in tissues. It has been shown that the pattern of precipitates changes if the pyroantimonate is added immediately as opposed to 4 hours after the tissue has been fixed in the standard fashion.[2] Thus it appears that sodium can move in post-mortem tissue. *In vivo* fixation should eliminate such movement and represent a more accurate portrayal of sodium distribution. The dual fixation method has been shown to produce the clearest picture of the alveolar capillary membrane, a fact supported by the observation that this technic preserves the phospholipid surfactant layer.[8]

The idea, as suggested by the results of this study, that collagen might sequester substantial amounts of sodium and water during shock is not new. Moyer and Dillon [13] suggested that this mechanism may explain the efficacy of electrolyte solution resuscitation in the treatment of various shock states. In a series of hemorrhage studies in rats and dogs, they showed that electrolyte solution plus shed blood resulted in higher survival rates than did a variety of other fluid combinations. This observation has been confirmed by a host of subsequent investigators. To test the hypothesis that collagen could take up sodium and water following stress, they studied the effect of burns and hydraulic pressure on rat tail collagen. The results indicated that increased amounts of both sodium and water were taken up by the collagen. The effects of



IG. 3b. High- power view of an area of the alveolar capillary membrane in a control lung. Note the discrete localization of sodium yroantimony deposits within the collagen fibers (× 39,600).

hemorrhagic shock on collagen was studied by Fulton *et al.*[7] They found that subcutaneously implanted colagen strips in dogs gained more sodium and water following hemorrhagic shock than did controls. The possible role of pulmonary collagen on lung function during shock was first suggested by Altschule.[1] He emphasized that high concentrations of collagen were present in the lung, being exceeded only by that of skin and gut.

Further evidence that substantial amounts of sodium may be taken up by the lung under conditions of stress was recently presented by Gump and associates.[9] They carried out a study in humans in which a bolus containng radioactive sodium, radioactive albumin, and tritiated water were injected simultaneously into a central vein and collected at frequent intervals from a peripheral artery. In control studies, approximately 95% of the injected sodium was recovered in a single pass through the lungs. Under conditions of stress, only 85% of the sodium could be recovered in a single pass, indicating that take-up of sodium in lung tissue had occurred. Mashima and co-workers[11] analyzed the lungs from patients who died from pulmonary insufficiency following nonthoracic trauma. They found increased amounts of pulmonary sodium in these patients, once again indicating take-up of sodium by the lung in shock.

The present study emphasizes the potential importance of the pulmonary collagen fibers. Originally they were thought to function only as a structural framework for the lung. Cotrell *et al.*,[3] in an ultrastructural study of hemodynamically induced pulmonary edema, pointed out that pulmonary edema begins in the thick portion of the alveolar capillary membrane in the areas occupied by collagen fibers. He proposed that these fibers might function as sponges to pick up excess interstitial water and thereby maintain the alveoli in a dry state. The fact that there is a delay in lymph flow from the lung during overinfusion-induced pulmonary edema supports the idea of initial water-binding by collagen.[16]

The findings in our study of dispersion of individual

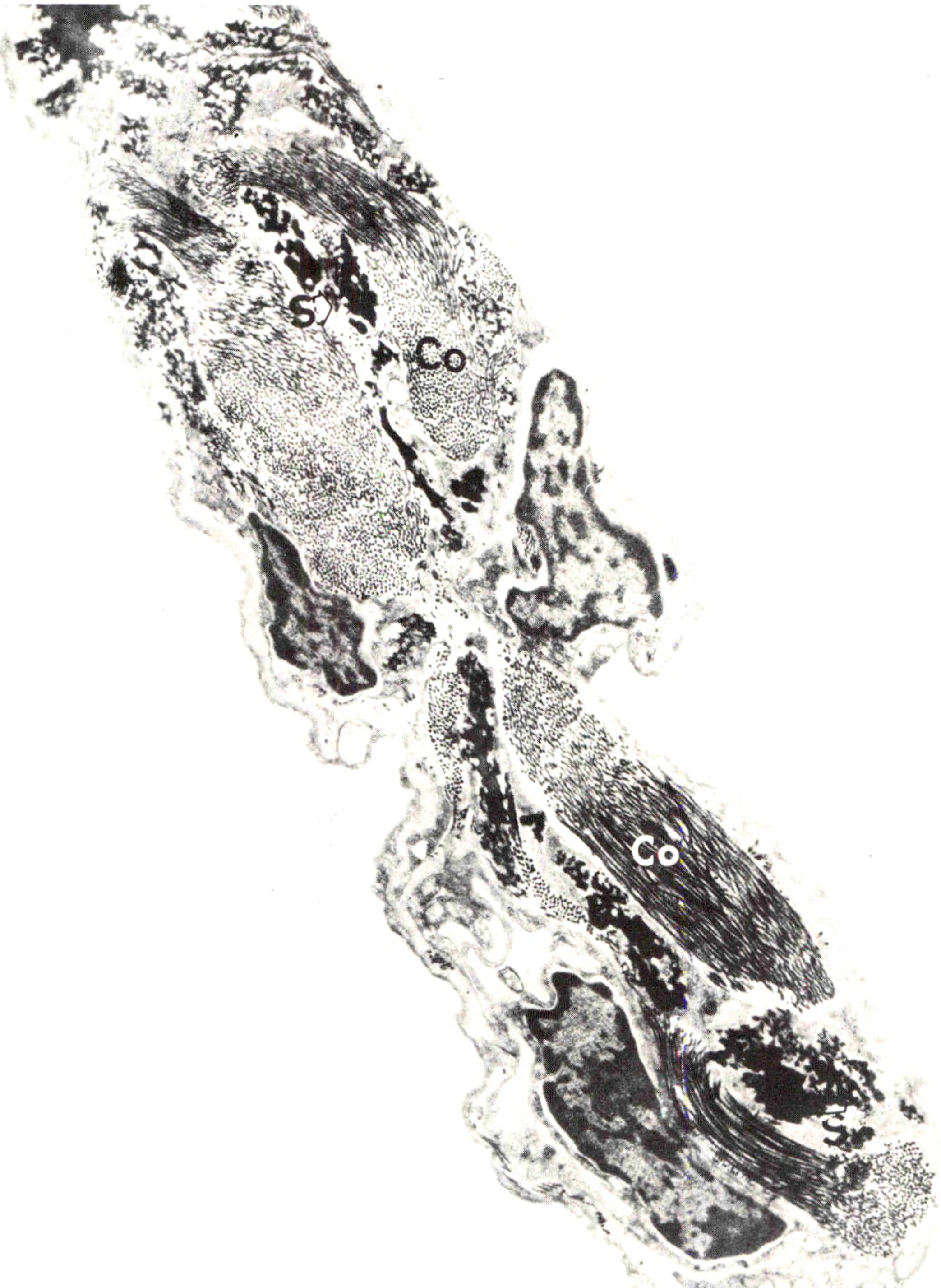


FIG. 4a. Low-power view of the alveolar capillary membrane in shock. The appearance of large areas of interstitial intensely-stained smudging (s) indicating sodium rich edema fluid. Dispersion of collagen fibers (CO) is obvious (× 15,370).

collagen fibers plus a major increase in sodium pyroantimonate precipitates in these same areas may represent at least a partial explanation for the development of postresuscitation pulmonary insufficiency often seen in patients suffering from severe trauma or hemorrhage. It is possible that the high concentrations of sodium developing in the interstitium and within individual collagen fibers during shock produce local osmotic gradients, which results in the transudation of plasma water into the interstitium and subsequent saturation of collagen water binding sites. During resuscitation, such sites could no longer function in a normal fashion to aid in the maintenance of dry alveoli. The result could be interstitial and alveolar pulmonary edema, a condition known

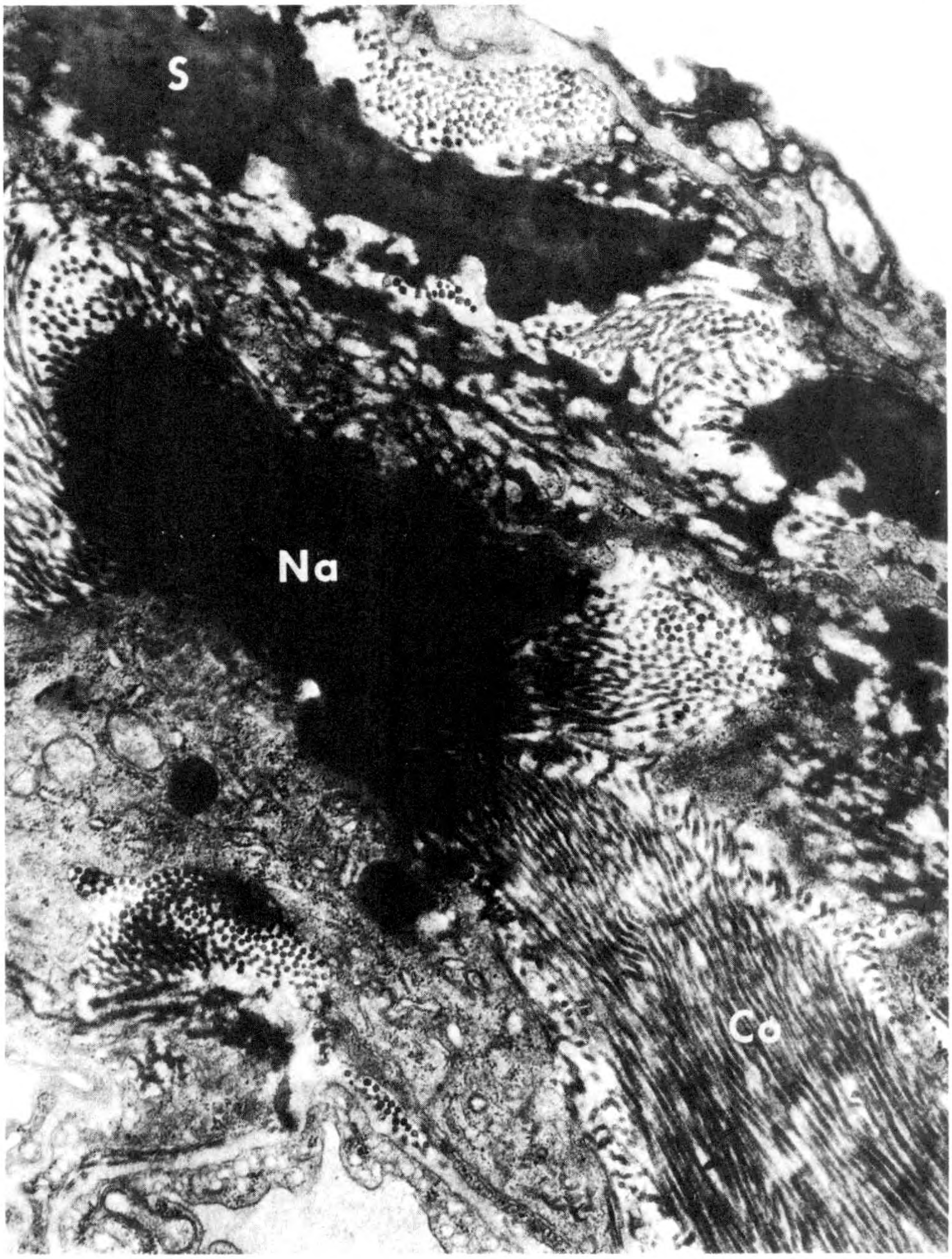


FIG. 4b. High-power view of one area showing spectacular deposition of sodium pyroantimonate as well as smudging in shock lung (×26,180).

to develop in man with the postresuscitation pulmonary insufficiency syndrome.

Summary

The ultrastructural distribution of pulmonary interstitial sodium was studied in the adult baboon in the control state and after 2 hours of hemorrhagic shock. Sodium was labeled by *in vivo* fixation of one lung with an aqueous solution of unbuffered potassium pyroantimonate. Perfusion fixation was carried out simultaneously through the vascular and endobronchial systems in the live animal.

In the control state, sodium precipitates were noted within endothelial pinocytotic vesicles, around groups of collagen fibers within the alveolar capillary membrane, and within individual collagen fibers. After 2 hours of hemorrhagic shock, the number of endothelial pinocytotic vesicles increased; a substantial increase in sodium precipitates was noted around and within the collagen fibers, and sodium rich edema fluid accumulated within the alveolar capillary membrane. No evidence of damage or disruption of the endothelial layer was observed.

It is concluded that 1) increased amounts of sodium and water accumulate in the alveolar capillary membrane during hemorrhagic shock, and 2) that these changes may help explain the development of pulmonary

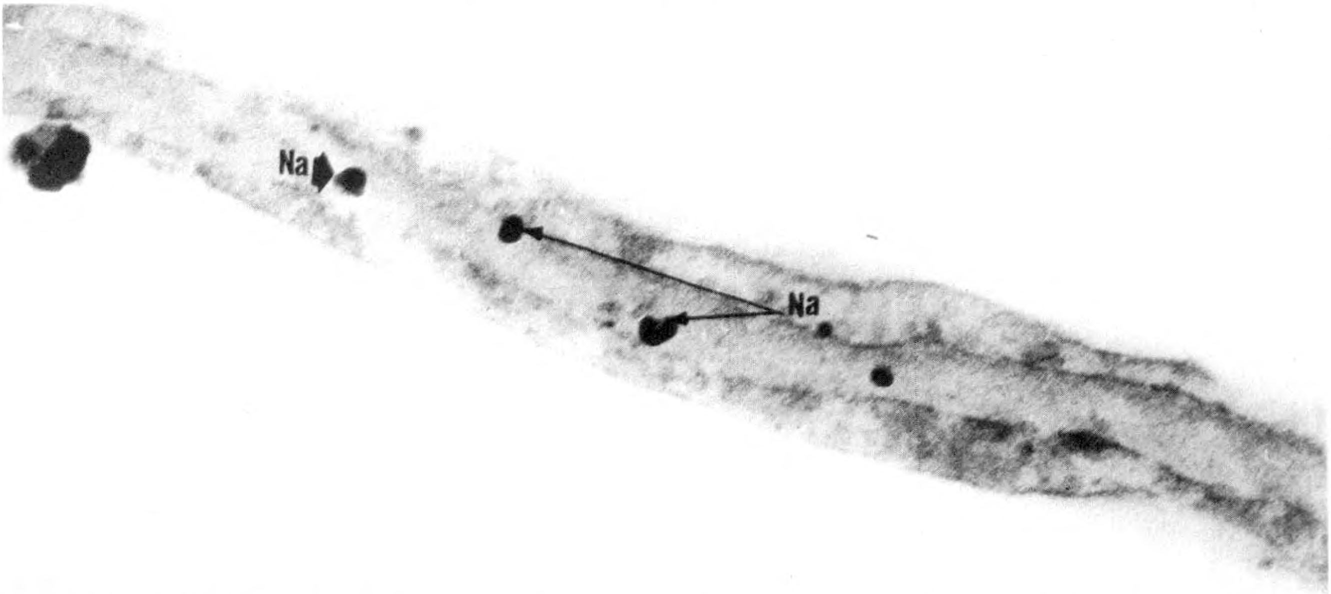


FIG. 5. The endothelial lining of a capillary in shock. Note the sodium pyroantimony deposits within the pinocytotic vesicles (× 43,200).

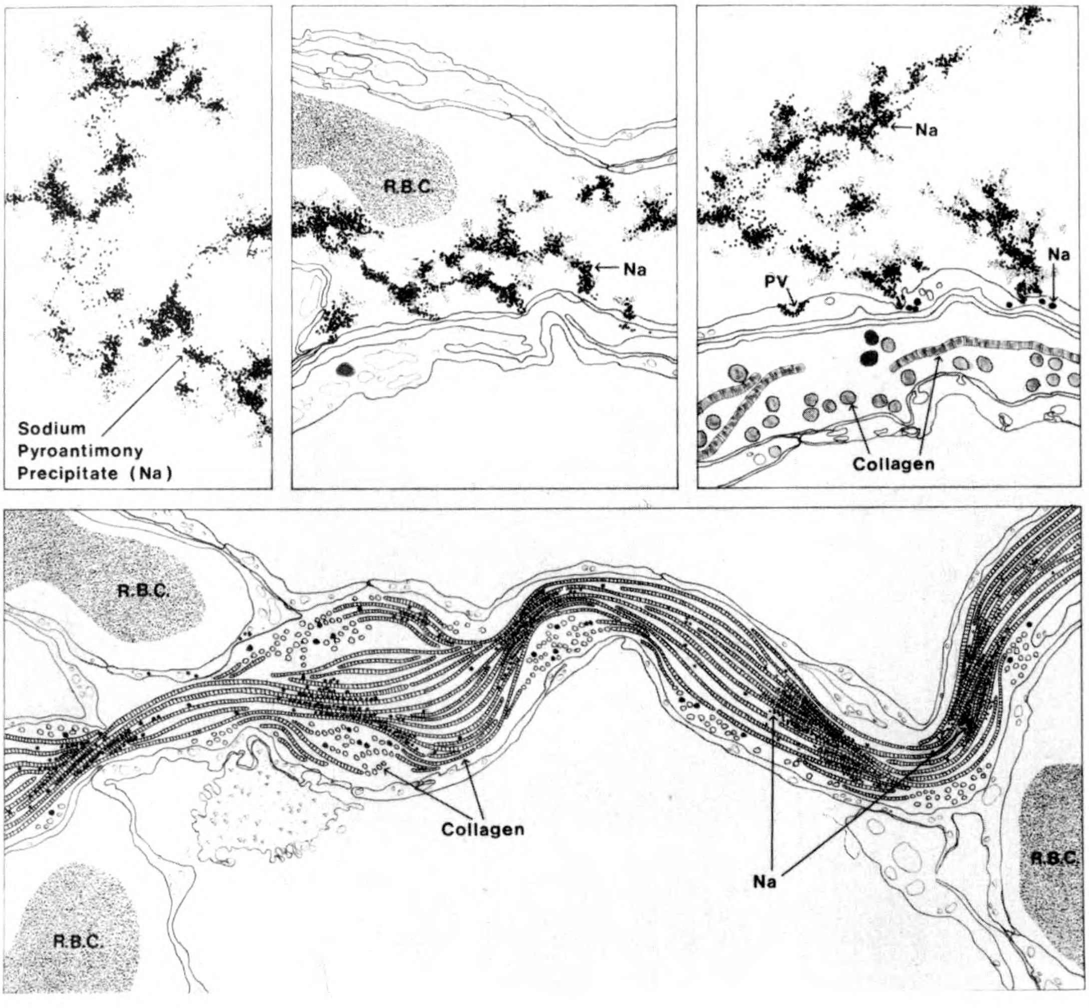


FIG. 6. Diagramatic rendition of the possible mode of endothelial transport of sodium and its ultimate distribution in the interstitial space of the alveolar capillary membrane of a control baboon lung. The upper left panel demonstrates the characteristics of sodium pyroantimony precipitate. The upper middle panel shows sodium within the capillary lumen, as well as the presence of the deposits within the pinocytotic vesicles. The upper right panel shows the discrete localization within the vesicles. Several vesicles are close to the basement membrane. The lower panel shows the distribution of sodium precipitates in and around the collagen fibers.

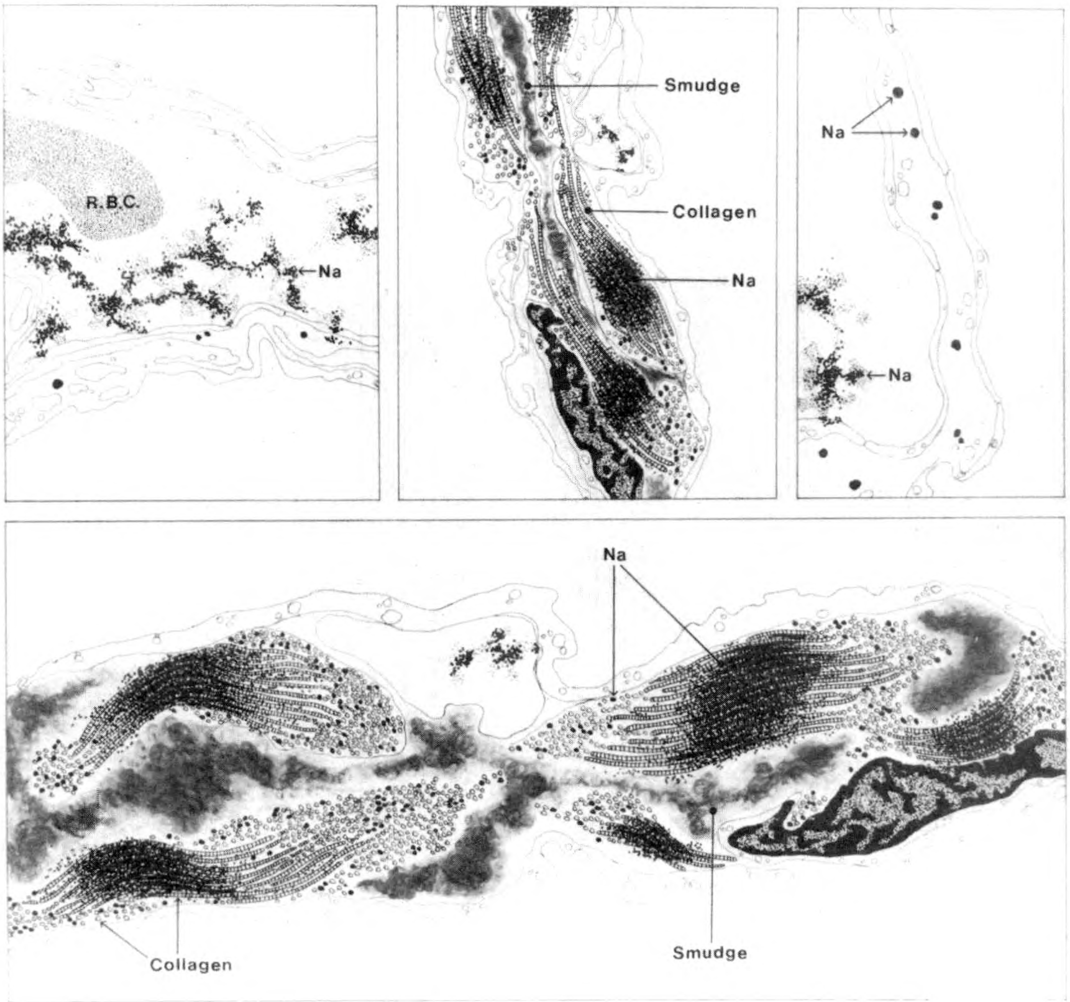


FIG. 7. Diagramatic rendition of the possible mode of endothelial transport of sodium and its final distribution in the interstitial space of the alveolar capillary membrane of a baboon lung in hemorrhagic hypotension. The left upper panel shows the distribution of sodium pyroantimonate precipitate in the capillary. Note the precipitates are also within pinocytotic vesicles and progressing to the interstitial space. In the upper middle panel a low-power view shows the massive profile of sodium pyroantimony precipitate within the collagen fibers and the intense smudging representing edema. In the upper left panel the migration of sodium pyroantimony precipitate via pinocytotic vesicles are seen and no migration through the intercellular junctions are noted. In the lower panel the intense smudging, massive deposition of sodium pyroantimony precipitates are graphically shown.

insufficiency in man following shock or nonthoracic trauma.

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Effects of Vitamin A and Glucocorticoids upon Inflammatio and Collagen Synthesi

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GLUCOCORTICOIDS inhibit collagen synthesis and connective tissue repair. The effect is best demonstrated when administration of the hormone begins just prior to or soon after injury.[6] Glucocorticoids are relatively ineffective in impairing fibroplasia in closed wounds once inflammation has become established.[5] Presumably, therefore, their action is mediated mainly by the anti-inflammatory action.

Vitamin A given concurrently can reverse the inhibitory effects of glucocorticoids on repair, as measured by tensile strength.[2] Vitamin A given alone slightly increases the rate at which collagen accumulates within an implanted polyvinyl sponge granuloma.[4] An excess of this vitamin has also been associated with the enzymatic breakdown of connective tissues.[7]

This study was designed to determine if the reversal by vitamin A of the effect of glucocorticoid coincides with reestablishment of inflammation and fibroplasia.

Methods

A. *Histological*

Ivalon® polyvinyl sponges, 1 cm. in diameter by 0.1 cm. in thickness were sandwiched between two silicone rubber discs (cut from silicone rubber stoppers) *, 1 cm. in diameter and 0.2 cm. thick. The three discs were secured together with a centrally located stitch. This technique was devised in order to eliminate cellular infiltration from the top and bottom surfaces. Cellular migration into the disc can occur only from the periphery to the center of the disc. Thus, when the disc is sectione parallel to its flat surface for histology, the spatial sequences from within to without are in chronological order.

Two silicone-sponge-silicone discs[1] were implante under the skin of male adult Sprague Dawley rat weighing 350 to 400 gm. They were fed a commercial ra chow and water ad libitum. The total group of 24 wa divided into 4 treatment groups of 6 rats each:

Group I, (Control). These rats received no injections.

Group II, (Corticoid alone). These rats received single injection of 8 mg of Depo Medrol® (prednisolon acetate, Upjohn Company) subcutaneously immediatel after implantation of the discs.

Group III, (Vitamin A alone). These rats receive injections of 5000 IU of vitamin A palmitate as 0.1 ml o Aquasol A® (U.S. Vitamin and Pharmaceutical Company) intramuscularly on the day of surgery and on day 2 and 4.

Group IV, (Combination). These rats received a injection of 8 mg of prednisolone acetate subcutaneousl and 5000 IU of vitamin A palmitate per injection intramuscularly on the day of surgery. Vitamin A was administered as in Group III.

Three and seven days following implantation, 3 rat from each treatment group were killed. The sandwiche implants were dissected out; the silicone discs were removed and fixed in a buffered 10% solution of formaldehyde. Microscopic sections were made parallel to th flat face of the disc and stained with hematoxylin eosin and Mallory phosphotungstic acid-hematoxylin whic differentiates between collagen fibers and fibrin.

For histological grading, four locations were uni

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TABLE 1. *Summary of 3-Day Histological Survey of Polyvinyl Sponge Disc Implants*

		I Controls N = 16	II Corticoids N = 6	III Vitamin A Alone N = 16	IV Corticoid and Vitamin A N = 16
1	Red Blood Cells	0.71 ± .27*	(1) 0	(3) 1.57 ± .25	(2) 0.86 ± .21
2	Fibrin	2.41 ± .29	1.82 ± .81	2.06 ± .25	2.38 ± .20
3	Polymorphonucleated Cells	2.56 ± .18	(1) 1.12 ± .15	2.62 ± .24	(2) 2.06 ± .21
4	Mononuclear Cells	0.25 ± .12	0.88 ± .18	0.25 ± .12	0.12 ± .12
5	Fibroblasts	2.0 ± .22	1.44 ± .32	(3) 2.9 ± 1.3	1.56 ± .13
6	Collagen Fibers	2.29 ± .29	(1) 1.75 ± .14	2.05 ± .27	1.69 ± .12

The numerical evaluation reported is the subjective grading for 0 to +4 of four separate areas on each sponge disc histological section examined under a light microscope.

* Standard Error

(1) Statistical significance between control group and cortiocoid alone group $p < 0.05$.

(2) Statistical signficance between corticoid plus vitamin A group and corticoid alone group $p < 0.05$.

(3) Statistical significance between control group and vitamin A alone group $p < 0.05$.

formly marked off with a grease pencil at 3, 6, 9, and 12 o'clock on each stained section. Each location was examined and evaluated by a number grade: Erythrocytes, polymorphonucleated cells, mononuclear cells, fibroblasts, collagen fibers, and fibrin were graded with a value of 0 for no evidence, a value of 1 for occasional evidence, a 2+ for a light scattering, 3+ for abundant evidence and 4+ for confluent cells or fibers. The totals for the histological sections were recorded and analyzed with the Student's t method.

B. *Collagen Accumulation*

Twenty rats were divided into four treatment groups as described in part A. Four polyvinyl sponge discs (without silicone disc ends) 1.0 cm. in diameter and 0.2 cm. thick were implanted under the skin of each rat. Seven days later the implants were carefully dissected out, leaving the thin dense tissue capsule in contact with the disc. The explants were dried to a constant weight in a drying oven, hydrolyzed in 6N HCl at 110°C for 24 hours, filtered through a glass paper, dried in a vacuum over NaOH pellets, and redissolved in distilled water. The hydroxyproline content of each hydrolysate was determined by the automated method of Grant.[3]

Results

A. *Histological*

The summaries of the numerical gradings of stained sections of the granulomas appear in Tables 1 and 2. At 3 days, the erythrocytes appeared to be normal, which diminishes the possibility that they were trapped within the sponge during implantation. No erythrocytes were seen in the three day wound in group II that received corticoid alone, which contained very few new capil-

TABLE 2. *Summary of 7-Day Histological Survey of Polyvinyl Sponge Disc Implants*

		I Control N = 8	II Corticoid Alone N = 16	III Vitamin A Alone N = 8	IV Corticoid and Vitamin A N = 8
1	Red Blood Cells	2.62 ± .18*	(1) 1.29 ± .27	2.00 ± .33	(2) 0.25 ± .12
2	Fibrin	2.50 ± .19	(1) 2.12 ± .12	1.25 ± .16	2.12 ± .12
3	Polymorphonucleated Cells	3.62 ± .26	(1) 1.75 ± .27	(3) 0.75 ± .16	(2) 1.00 ± 0
4	Mononucleated Cells	2.12 ± .29	(1) 0.88 ± .23	(3) 1.38 ± .26	1.12 ± .12
5	Fibroblasts	2.62 ± .18	(1) 1.44 ± .20	(3) 4.00 ± 0	(2) 2.40 ± .32
6	Collagen Fibers	2.75 ± .25	(1) 1.69 ± .22	(3) 4.00 ± 0	(2) 3.00 ± .19

The same subjective grading system as Table 1.

* Standard Error

(1) (2) (3) These numerals are explained in Table 1.

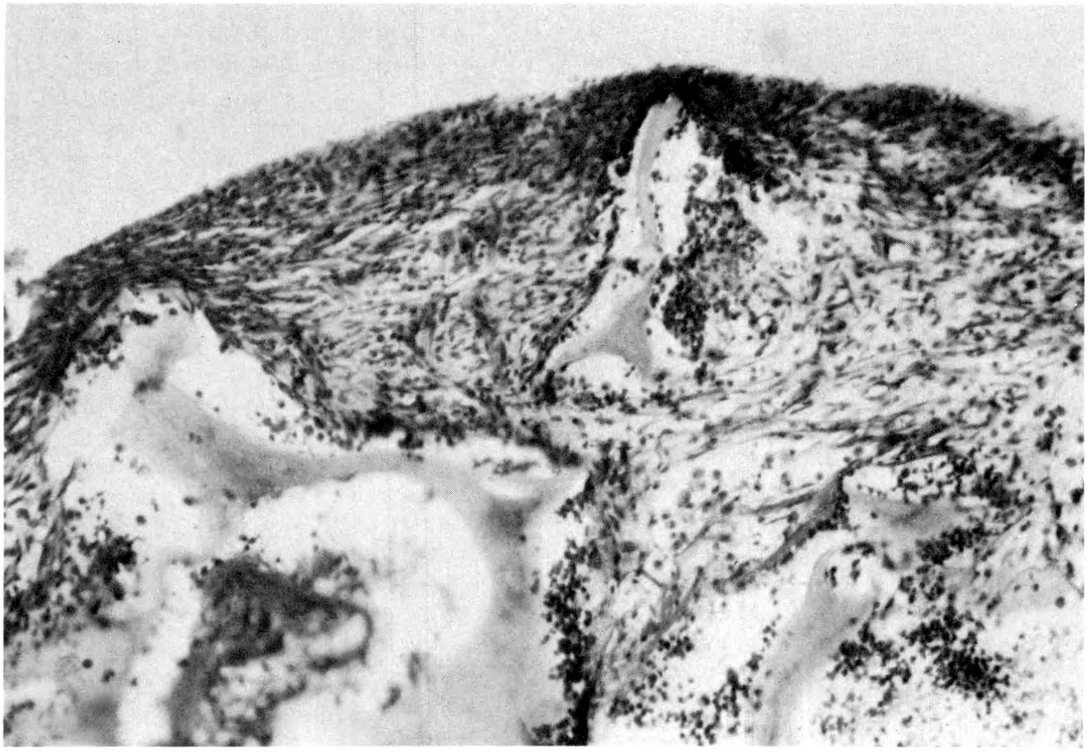

FIG. 1. Photomicrograph of sponge implant at 7 days in control group I. Collagen and fibroblasts fill the outer interstices in the polyvinyl sponge. Inflammatory cells, fibroblasts and fibrin are seen more centrally.

laries. The group treated with vitamin A alone contained the most capillaries and also had the greatest number of free erythrocytes.

The fibrin content appeared similar in all groups at 3 days.

Polymorphonucleated cells (PMN) were the most abundant phagocytic leukocyte seen early after injury. At three days, the corticoid alone group (II) had the least number or PMN cells while the combination group (IV) showed a significant increase over group II (corti-

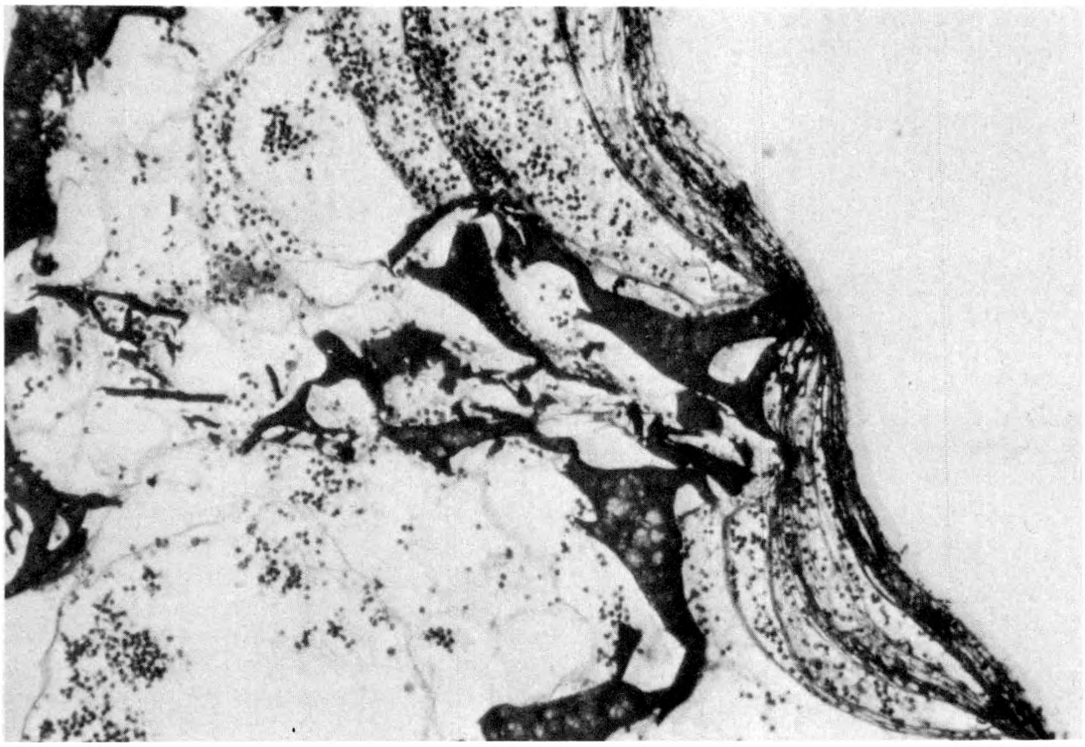

FIG. 2. Sponge implant at 7 days in group II, corticoid treated. A scanty inflammatory reaction and fibrin occupy the outer interstices of the polyvinyl sponge. Few, if any, fibroblasts and no collagen can be seen.

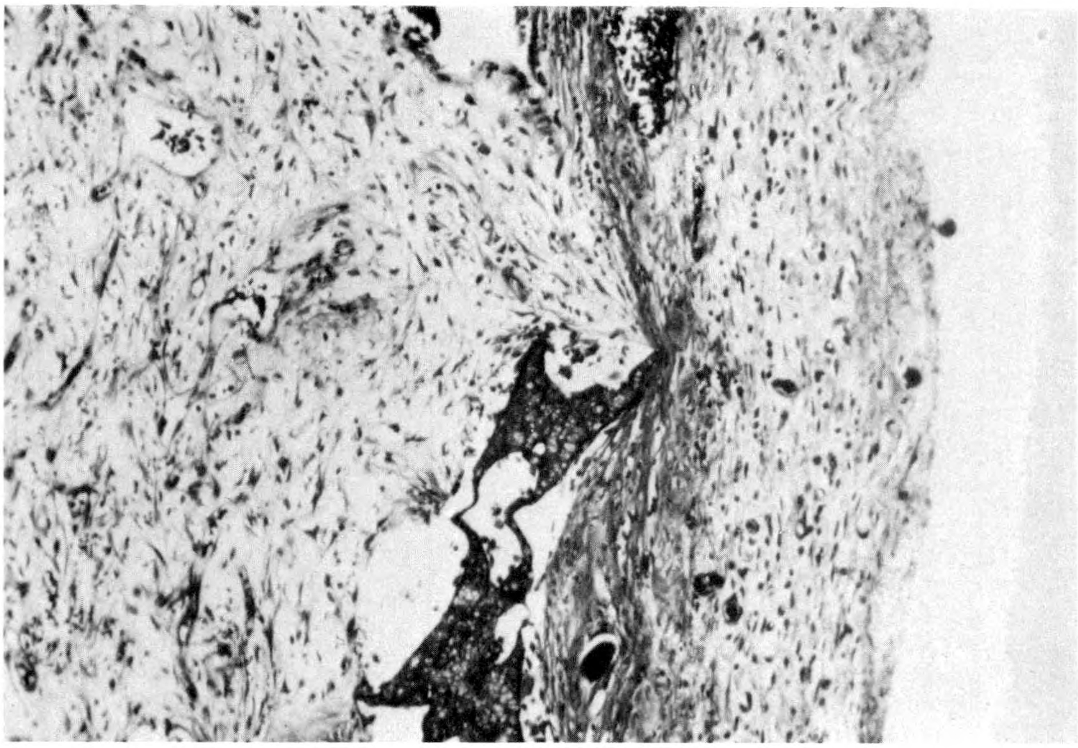

FIG. 3. Sponge implant at 7 days in Vitamin A alone group (III). The outer "capsule" is shown. New collagen, fibroblasts, inflammatory cells, and new vessels are seen filling the outer interstices.

coid treated). Apparently, vitamin A reinstituted the infiltration of PMN cells in the presence of glucocorticoids. However, the group that received vitamin A alone (Group III) appeared to have no greater number of PMN cells than the control group (Group 1).

Mononucleated cells, which are a mixture of macrophages, primitive mesenchymal cells, and immature fibroblasts, were counted as "mononuclears". Their relatively small number as compared to PMN cells makes it difficult to evaluate their importance.

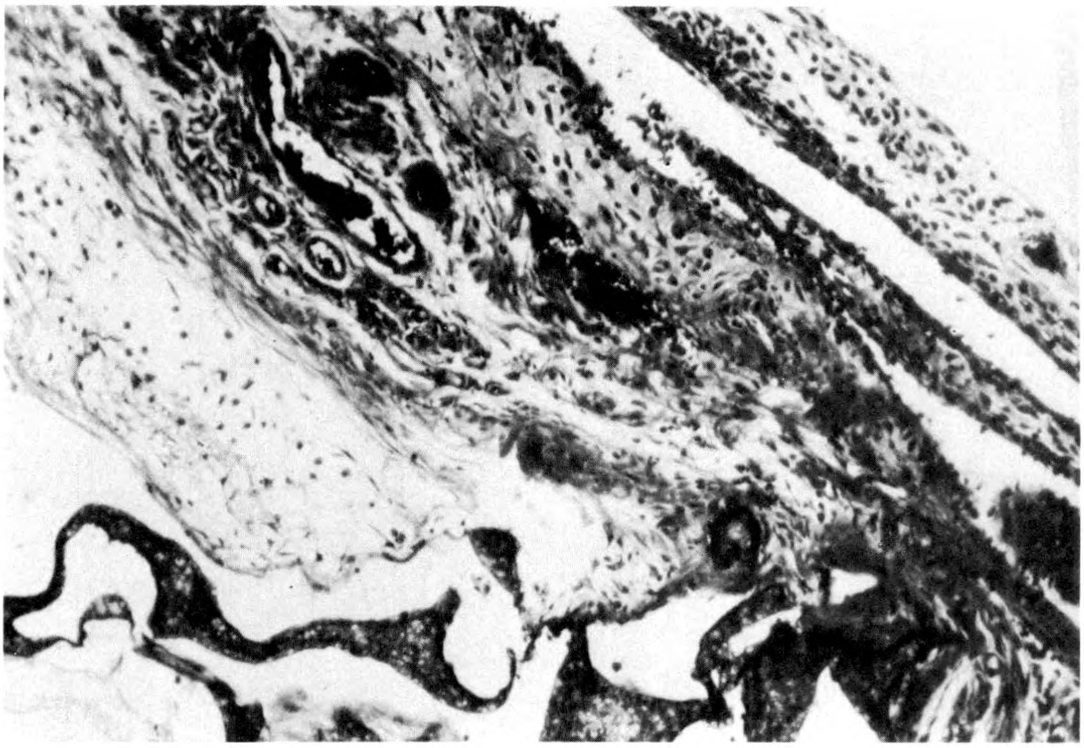

FIG. 4. Sponge implant at 7 days in the corticoid and Vitamin A group (IV). Some "Capsule" is shown. The outer interstice is filled with new tissue and collagen. The inflammatory reaction is visible but is not as extensive as normal.

TABLE 3. *Summary of Vitamin A Palmitate and Prednisolone Acetate Effect upon Collagen Synthesis as Measured by Hydroxyproline in a Polyvinyl Sponge Granuloma*

	I Control	II Corticoid alone	III Vitamin A	IV Combination
Total Hydroxyproline in μg ± S.E.	543 ± 28	306 ± 21*	594 ± 26*	409 ± 22*
Sponge dry weight (mg)	59 ± 2.3	38 ± 2.8*	55 ± 2.1	44 ± 2.7*
Micrograms hydroxyproline Miligrams dry weight of sponge	9.9	8.1*	10.8*	9.1*

* Values are significantly different from controls $p < 0.05$.

At three days there was a significant absence of fibroblasts in the corticoid group (II). There were more fibroblasts in the combination group (Group IV) but the number was less than normal. The animals that received vitamin A alone (Group III) had a significant increase as compared to the control animals (Group I).

Because of the design of the sandwiched sponge implant, the depth of the collagenous invasion at the periphery of the disc is proportional to the total collagen content. The depth of invasion was also proportional to the accumulation of fibroblasts at 3 days. There was one exception, however, to the correlation between the deposition of collagen fibers and number of fibroblasts. In the animals that were given vitamin A alone (Group III), at 3 days we failed to note a significant increase in the amount of collagen fibers as compared to control animals (Group I), even though there was a significant increase in the number of fibroblasts.

In the corticoid group (Group II), the number of cells and collagen fibers is depressed as compared to the other groups. Vitamin A partially reversed the effects of corticoid. At seven days scattered intact erythrocytes and some capillaries appeared in animals that received corticoids (Group II). (Table 2). The amount of fibrin in the animals given vitamin A alone (Group III) was reduced, which appears to be the result of its replacement by collagen fibers and fibroblasts. Polymorphonucleated cells began to accumulate by seven days in the animals that received corticoid alone (Group II). PMN cells were reduced in the two groups that received vitamin A as compared to the control animals (Group I). This seems to be a consequence of the replacement of PMN by fibroblasts and collagen fibers. The relative number of mononuclear cells was similar in all four treatment groups. The retarding effects of glucocorticoid therapy upon fibroplasia were still evident at 7 days. The animals that received corticoid alone (Group II) had fewer fibroblasts as compared to the combination group (Group IV); but vitamin A did not completely reverse the effects of corticoids. The sponges in the animals in Group III still contained a significantly higher number of fibroblasts. The collagen content correlated well with the number of fibroblasts in all groups. Group III at seven days showed an increased deposition of collagen fibers which correlated well with its significant increase in the number fibroblasts.

Representative sections from the four treatment groups on the seventh day appear in Figures 1 through 4. In general there is an increase in the amounts of cells and tissue as compared to 3 days in all four treatment groups. The inhibitory effects of glucocorticoid therapy and the stimulatory effects of vitamin A are still evident.

B. *Collagen Accumulation*

The results are summarized in Table 3. The inhibitory effects of glucocorticoids are manifested by the reduced dry weight and hydroxyproline content of sponges in Group II. The concurrent administration of vitamin A, as shown in group IV, significantly restored collagen accumulation toward control levels. Unlike the data on tensile strength previously reported, however, vitamin A did not restore collagen accumulation completely to normal.[2] The sponges in Group III (vitamin A alone) contained increased amounts of hydroxyproline, which is in agreement with the report of Herrmann and Woodward.[4]

Discussion

The administration of glucocorticoid immediately after surgery alters many aspects of repair. The major changes include reduced inflammatory cell infiltration and fibroplasia and a decrease in new capillary budding and deposition of collagen fiber. The concurrent administration of high levels of vitamin A returns these histological and biochemical parameters back toward normal quantity and sequence.

When glucocorticoid therapy is withheld until after the third day following injury, healing as measured by tensile strength at seven days is not impaired.[5] Glucocorticoids are less effective in inhibiting repair after inflammation has been established. This time-dose effect coupled with our histological findings which show that vitamin A partially restores inflammation supports the assumption that corticoids inhibit healing by impairing inflammation and fibroplasia rather than by merely inhibiting fibroblasts from synthesizing collagen. The total number of fibroblasts was decreased in the wounds of rats treated with glucocorticoids. Since hydroxyproline was found in these sponges, the few fibroblasts that were there were able to synthesize collagen. Therefore, the primary effect of glucocorticoids was to reduce the accumulation of fibroblasts. Vitamin A, on the other hand, stimulates fibroplasia, resulting in a greater accumulation of collagen. Vitamin A does not appear to cause an increased inflammatory response to injury as measured by the number of infiltrating polymorphonucleated leukocytes. In the presence of glucocorticoids, vitamin A stimulates the inflammatory response toward normal. More importantly, vitamin A given concurrently with glucocorticoids will stimulate fibroplasia, resulting in a significant increase in the deposition of new collagen.

Conclusions

Glucocorticoids inhibit the inflammatory response to injury and the rate at which fibroblasts accumulate in wounds. Vitamin A reverses the retarding effects of glucocorticoids on collagen accumulation. When given concurrently, vitamin A restores corticoid-inhibited inflammation toward normal. Excess vitamin A alone mildly stimulates fibroblasts and collagen accumulation.

Acknowledgments

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Granular Cell Myoblastoma of Stomach

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GRANULAR CELL MYOBLASTOMAS are among the rarest of tumors which occur in the gastric wall. Because of this rarity the surgical literature contains no report of this lesion. Questions regarding the etiology, natural history and surgical management of these unusual tumors have prompted a review of the literature and this report of a patient with gastric granular cell myoblastoma.

Case Report

A 32-year-old, married, Negro woman entered the UCLA Emergency Room on November 30, 1971, after 2 hours of dull, mid-epigastric pain with radiation to the right lower quadrant. The pain was constant with intermittent cramping and was associated with anorexia, nausea, vomiting, and several loose bowel movements. It bore no relationship to meals or activity. Past history disclosed that the patient had suffered three such episodes in the previous 3 months which were not constantly related to menses. She had been hospitalized twice for evaluation at another hospital for the preceding two attacks. Studies there had included a normal oral cholecystogram, barium enema and intravenous pyelogram. An upper gastrointestinal series on October 7, 1971, had demonstrated a 1.0 cm. × 1.5 cm. polypoid lesion in the fundus of the stomach lateral to the entry of the esophagus. The radiologist interpreted the lesion as being pedunculated (Fig. 1). The remainder of past history, family history and review of systems was noncontributory. Physical examination on the present admission disclosed normal temperature, pulse, blood pressure, head, eyes, ears, nose, throat and chest findings. Epigastric guarding and right lower quadrant tenderness without rebound were found in the generally soft abdomen. No masses or organomegaly were felt. Right adnexal tenderness was present on pelvic exam, but no masses were identified. Rectal examination showed tenderness high on the right side. Abdominal and chest x-rays were unremarkable. The white blood cell count was 6,900 with a normal differential, and a serum amylase determination was also normal. The patient was observed in the hospital for 20 hours during which time the epigastric pain subsided and the patient subjectively improved. There had been no elevation of temperature or leukocyte count; however, point tenderness in the right lower quadrant became pronounced. Exploratory laparotomy was performed through a lower midline incision with a preoperative diagnosis of acute appendicitis. The appendix was turgid and moderately inflamed but with no evidence of perforation. It was packed away with moist pads and the incision extended cephalad. A longitudinal gastrotomy revealed a sessile gastric mass 1.5 cm. × 1 cm. × 1.2 cm. on the lesser curvature of the proximal third of the stomach. The mucosa over the lesion was intact and was excised with the mass. Frozen section diagnosis was granular cell myoblastoma. An adjacent smaller mass (0.4 cm. diameter) was biopsied but showed no evidence of tumor. The gastrotomy was closed and appendectomy carried out. Final pathological sections (Fig. 2) confirmed the frozen section diagnosis of granular cell myoblastoma as well as the preoperative diagnosis of acute appendicitis. The patient's postoperative course was benign and she was discharged on the ninth postoperative day.

Discussion

Granular cell myoblastoma is a rare, usually benign tumor which most commonly (50%) arises in the skin, subcutaneous tissue or breast. The tongue is the site of origin in an additional one-third of the cases.

These tumors are even less common in the stomach. Although eight cases have been reported previously in pathology and radiology journals,[2,7,9,12,13,14] the surgical literature contains no reference to this gastric tumor. The present case is thought to be the ninth well-documented report in the English literature.

The embryology and histiogenesis of this tumor remain a much disputed topic. Although originally described by Abrikossoff[1] as arising from the myoblast or adult muscle cell precursor, this origin of the tumor is now disputed. As summarized by Strong, McDivitt and Brasfield[14] current theories of origin include: a non-neoplastic product of trauma, degeneration and regen-

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ation; a storage or metabolic disorder involving histio-
tes; a neoplasm of myogenic, neural, fibroblastic or
esenchymal origin; and finally, a tumor of multicellu-
r origin.

Typically, granular cell myoblastomas present as sim-
le small nodules which are fairly well demarcated from
rrounding tissues and on cut section show a yellow-
hite, firm, uniform tumor, occasionally appearing to
encapsulated. Histologically, the tumor is composed
irregular, polyhedral cells arranged in bundles, sheets
cords. The cytoplasm is pale to densely eosinophilic
id quite granular. An inconspicuous fibrous supporting
roma is usually present.

As noted in Table 1, two of the nine cases of granular
ll myoblastoma occurring in the stomach lack signifi-
int clinical presentation for critical comparison and
valuation.[13,14] One patient had shortness of breath,
eakness, weight loss, occult blood in the stool and
norexia. The remaining six patients (including the
resent) all had epigastric pain occurring intermittently
r 1 week to 10 years.[2,12,9] Four of the patients had
pical peptic ulcer symptoms.[2,7,12]

Studies of one patient[7] who had abdominal pain
vealed gastric cytologic findings suggestive of malig-
ancy. Gastric analysis showed free acid only after
istamine stimulation. Despite demonstration on upper
astrointestinal series of two lesser curvature gastric
lcers, there was no evidence of active or healed gastric
lceration at the time of gastrectomy. A small, oval
aped submucosal nodule 0.9 cm. × 0.6 cm. × 0.4 cm.
as excised from the posterior wall of the mid-stomach
ear the lesser curvature. It was postulated that the sus-
icious gastric cytology may have been due to pseudo-
pitheliomatous hyperplasia of the gastric mucosa
milar to the well-described changes which occur in the
pithelium of the tongue overlying a granular cell myo-
lastoma.[7,11]

The first of Schwartz and Gaetz's[12] two patients had
n upper gastrointestinal series revealing multiple filling
efects up to 3 cm. in diameter in the fundus and pars
edia of the stomach which were interpreted as multi-
le gastric polyps or lymphosarcoma by the radiologist.
astric aspirate from this patient contained only five
egrees of free acid, 30 minutes after histamine stimula-
on. At operation, five discrete, nonencapsulated, firm
ubmucosal nodules up to 2.5 cm. in diameter were
ound attached to the overlying mucosa. Histologic ex-
mination of the 90% gastrectomy specimen revealed
ve granular cell myoblastomas. This is the only report
f multiple granular cell myoblastomas in the stomach.
chwartz and Gaetz's[12] second patient had multiple fill-
ng defects on the greater curvature of the stomach. Patho-
ogic examination of the resected middle third of the
tomach demonstrated adenomatous polyps 0.8 cm. to 2.5 cm. in diameter. A 1.8 cm. × 0.8 cm. submucosal nodule fixed to the overlying mucosa was found in the proximal gastric remnant and excised locally. This lesion proved to be a granular cell myoblastoma.

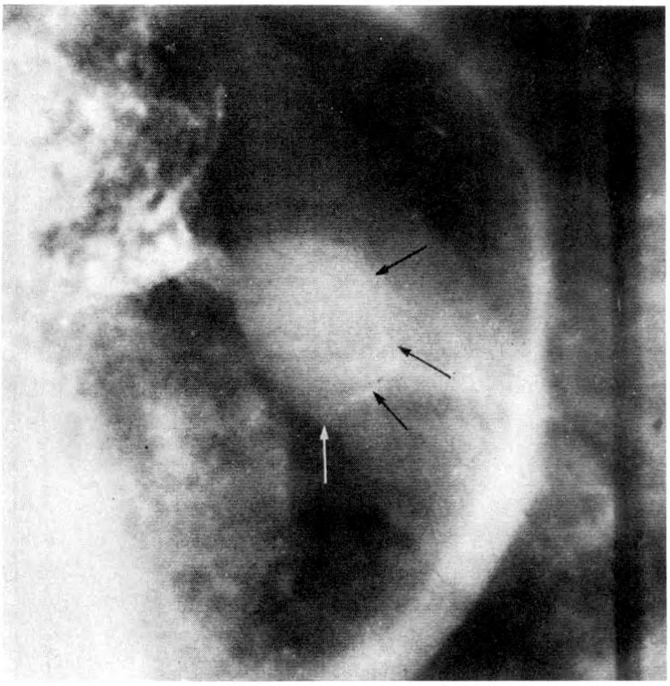

FIG. 1. Arrows outline the border of the pedunculated appearing polypoid lesion in the fundus of the stomach.

Both of the patients reported by Naidech, Axelrod and Seliger[9] were operated upon for gastric lesions demonstrated on UGI series. One showed a 4 cm. tumor mass of the pars media with central ulceration. The other

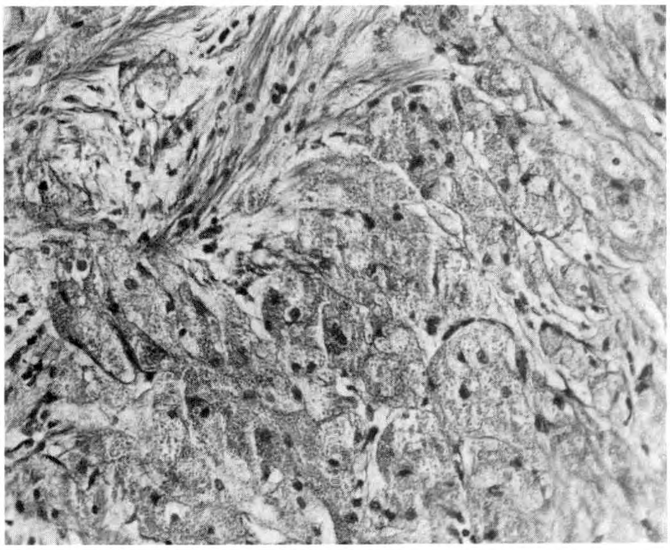

FIG. 2. Histological section of the lesion from the fundus of the stomach shows the typical irregular polyhedral cells arranged in bundles, sheets and cords. The prominent granular cytoplasm is noted. An inconspicuous fibrous supportive stroma is present.

TABLE 1.

	Age	Sex	Race	Symptoms	UGI	Surgical Findings	Operation
Stout[13] 1953						Small nodule in submucosa of cardia	
Azzopardi[2] 1956	46	M		Ten years mild intermittent epigastric pain relieved by food and alkali	None	Sessile subserosal nodule 1.0 × 0.8 cm. superior aspect pylorus	Local excision
Goodman, Gottlieb and Zamcheck[7] 1962	48	F	Negro	Progressive shortness of breath, weakness, weight loss, anorexia	Two gastric ulcers on lesser curvature	Subserosal nodule 0.9 × 0.6 × 0.4 cm. posterior wall in mid stomach near lesser curvature	Gastrectomy
Schwartz and Gaetz[12] 1965	39	M	Negro	Four months mild epigastric pain relieved by food, vomiting	Multiple filling defects up to 3 cm. diameter in fundus and pars media	5 submucosal nodules up to 2.5 cm. diameter fixed to overlying mucosa	90% gastrectomy and gastroduodenostomy
	44	M	Negro	Two months crampy epigastric pain and vomiting, 20 lb. weight loss	Multiple filling defects on greater curvature	5 adenomatous polyps 0.8 to 2.5 cm. greater curvature. Lesser curvature nodule 1.8 × 0.8	Sleeve resection of mid 1/3, pyloromyotomy and gastrogastrostomy
Strong, McDivitt and Brasfield[11] 1970							Radical excision
Naidech, Axelrod and Seliger[9] 1971	32	F	Negro	One year epigastric pain, weight loss, melena, anemia	Large intramural mass with a central ulceration in pars media	4 cm. tumor mass with 2 cm. central ulceration	Partial gastrectomy
	31	F	Negro	One week epigastric pain and vomiting	1.0 cm. nodule on lesser curvature near the incisura	1 cm. submucosal nodule	Local excision
Aston and Tompkins (pres) 1972	32	F	Negro	Three months intermittent epigastric and rt. lower quadrant pain	1.0 × 1.5 cm. polypoid lesion in fundus lateral to entry of esophagus	1.5 × 1.2 × 1.0 cm. sessile submucosal nodule	Local excision

patient had a 1 cm. rounded nodule on the lesser curvature of the stomach near the incisura.

Azzopardi's[2] patient was not reported to have had an upper gastrointestinal series but at operation was found to have a 1.0 cm. × 0.8 cm. sessile nodule in the anterior pyloric area. Microscopically, the granular cell myoblastoma involved the submucosa as well as sent collections of granular cells into the fibrous septa between the muscle bundles of the pylorus.

Until the present, granular cell myoblastoma has not been included in the differential diagnosis of patients presenting with the symptoms and radiologic findings listed in Table 1. It is of interest to note that all of those patients with granular cell myoblastoma of the stomach in whom race has been reported have been Negroes.

A most difficult problem arises when the surgeon receives a frozen section report of granular cell myoblastoma and is required to make a decision as to the proper operative procedure. The infrequency of this tumor in the stomach and the resulting unfamiliarity of most surgeons with this lesion can make this a perplexing decision. As noted in Table 1, three of the nine reported cases had simple local excision of the tumor nodule, one had a radical local excision and four underwent some type of gastrectomy.

None of the nine cases of granular cell myoblastoma of the stomach have been malignant. By far the majority of granular cell myoblastomas in all locations are considered to be benign. Although few, malignant granular cell myoblastomas are well-documented. Ross and Miller, in 1951[10] extensively reviewed the literature of reported malignant granular cell myoblastomas and concluded that only four cases were unequivocal. Gamboa[6] reviewed the world literature four years later and listed only ten authentic examples of malignant granular cell myoblastomas, none of which occurred in the gastrointestinal tract. The latter author divided the malignant variety of granular cell myoblastoma into two types, (1) a clinically malignant, histologically benign type and (2) a clinically and histologically malignant type. The prognosis was the same in both types with the patient usually succumbing to generalized metastases within 5 years of diagnosis. He noted that this tumor preferred the lymphatic mode of spread but that blood stream metastases were also seen. Svejda and Horn[15] reported a patient who underwent excision of a right groin tumor and 3 'ears later died with metastatic granular cell myoblas-oma in the small intestine, bladder, peritoneum, mesen-ery, omentum, epicardium, pericardium, pleurae, lymph iodes, lungs, liver, abdominal wall and thigh muscles. ;olberg[3,4] in 1962, reported a review of 400 cases of ;ranular cell myoblastoma containing only 14 malignant umors. Subcutaneous tissue was the primary site in iine of the cases, with the breast, eye lid, bladder and bi-eps being the other primary locations. One malignant umor occurred in the colon in this series.

Since a large number of patients with granular cell nyoblastoma of the stomach has not been reported to late, the general approach to the gastric variety of this umor should be based on the gross appearance of the esion. When a frozen section diagnosis of granular cell nyoblastoma is made at the time of excision of a lesion rom the stomach, the surgeon should be assured that the nargins of the resected specimen are clear. Many of hese tumors spread into local tissue planes and may ecur locally. Unless a lesion appears to invade adjacent tructures such a wide local excision should be adequate ince the vast majority are benign. Radical surgery based n a frozen section diagnosis of malignant granular cell nyoblastoma probably should not be done. As pointed ut by Friedman and Hurwitt[5] in discussing granular ell myoblastoma of the breast, the tendency of this umor to form syncytial cords and sheets and to infiltrate he surrounding tissue may prompt a misleading diagno-is of malignancy. However, if permanent sections show umor extending to the limits of resection with cellular typism, mitoses and a disorganized cellular pattern, he tumor should be considered potentially malignant nd reoperation performed with radical excision.[3,4] Vhen positive lymph nodes are present at the time a rimary gastric granular cell myoblastoma is diagnosed, t is doubtful if radical surgical treatment will be of enefit. The widespread metastases seen in the malig-iant forms of this tumor indicate a potential for rapid lissemination. There has been no benefit observed from adiation in these tumors.[8,11] There are no data available n the literature to indicate whether chemotherapy vould be of any value.

Summary and Conclusions

1. A ninth patient with benign granular cell myo-lastoma of the stomach is reported.

2. Although unusual, granular cell myoblastoma should e considered in the differential diagnosis of patients vith abdominal pain and radiographic gastric filling defects. The diagnosis should be more strongly considered in Negro patients.

3. Although potentially malignant, nine reported cases of granular cell myoblastoma of the stomach have been benign.

4. Unless the lesion appears to invade adjacent structures or there is histological evidence of malignancy, wide local excision would appear to be adequate surgical treatment.

5. Radical surgery should not be performed solely on the basis of a frozen section diagnosis of malignant granular cell myoblastoma of the stomach.

6. Radiation therapy has been of no significant benefit in treating malignant granular cell myoblastomas of other organs. The role of chemotherapy has not been assessed in the treatment of malignant forms of this tumor.

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Femoropopliteal Bypass with Reversed Autogenous Vein

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REVERSED AUTOGENOUS femoropopliteal venous bypass grafts have been employed at Saint Louis University Hospitals since 1966 for the treatment of femoropopliteal occlusive disease. This method of reconstruction has been utilized in preference to prosthetic bypass believing that experimental and clinical studies[4,10,12,18] have shown a poor long-term patency rate when synthetic material was utilized to bypass the occluded superficial femoral artery. Similarly, thromboendarterectomy has been reported to have a poor early and late patency rate.[5,8] *In situ* saphenous vein grafts were utilized early in our experience and were found to have a high rate of late occlusion.[2]

During the period from January 1966 to July 1971, 123 reversed autogenous femoropopliteal, venous grafts were employed to relieve arterial occlusive disease of the lower extremity and are the subject of this report.

Material

The 123 grafts were performed on 105 patients. The patient population consisted of 79 men and 26 women; this reflects a veteran's hospital population in which 56% of the operations were performed. The average age of the patients at the time of operation was 62 years with the range being 36–92 years. Twenty-three patients (21%) had previous diagnoses of myocardial infarction, and 38 patients (36%) were diabetic. Aorto-iliac atherosclerotic disease was evident clinically or radiographically in 38 patients with 11 patients (10%) underdoing aorto-iliac reconstruction prior to lower extremity grafting.

There were 65 procedures performed on the right leg and 58 on the left leg. The indications for operation included claudication in 49 extremities (42%), rest pain in 19 (10%), gangrene in 52 (46%) and aneurysm in three (2%). Claudication was of such a degree as to interfere with the patients' normal routine or occupation. Rest pain was defined as ischemic pain at rest with impending tissue loss. Patients with gangrene included those with non-healing ischemic ulcers as well as those with frank gangrene of the toes.

The vein graft joined the proximal popliteal artery in 64 legs (52%), and the distal popliteal below the knee joint in 59 legs (48%). The vein was placed along the course of the superficial femoral artery in 108 grafts and subcutaneous in 15 extremities. All anastomoses were performed after systemic heparinization in the manner described by Kunlin.[11] Anticoagulants were not used postoperatively.

The degree of disease in the popliteal outflow was graded by one of the authors (H.B.B.) in all extremities based on the preoperative or intraoperative arteriogram. Two grading systems were utilized. In one classification the outflow tracts were designated as three vessel, two vessel, one vessel and no vessel (isolated popliteal segment). The other method of grading outflow was that described by Morton *et al.*[14] The two systems are compared in Table 1.

Current follow-up is available on 115 grafts (91%) with eight grafts in five patients lost to follow-up. Patency was based on the presence of a palpable pulse, either in the graft or distal to it. Arteriograms were employed when patency was uncertain.

Results

Patency rates for 115 reversed, autogenous femoropopliteal vein grafts are presented in Table 2. The life

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table method of evaluation described by Stokes, *et al.*[16] was utilized to determine patency rates in all analyses. The overall patency rate at 1 year was 80%, and only three grafts occluded after that time, one 54 months after placement.

There were five hospital deaths, accounting for six grafts, resulting in an operative mortality of 5%. Three patients died from myocardial infarction, two having had previous emboli, and another died of gram negative sepsis from an unrecognized seminal vesicle abscess.

Numerous factors affect early and late patency rates including the clinical stage, outflow, length of the graft as well as quality and size of the vein. All of these factors can be readily evaluated except the latter. Vein size was recorded at the time of operative procedure in 80 of the 123 procedures and was greater than 5 mm. in diameter in 27%, less than 5 mm. in 38% and unknown in 35%. However, vein size does not indicate the quality of the vein; and large veins, not infrequently, were found to have local areas of fibrotic stenosis which required repair either at the initial operation or at a subsequent revision. Conversely, veins less than 5 mm. in diameter and free of disease could function adequately.

Short and long-term patency rates were similar whether operation was undertaken for claudication or for rest pain and gangrene (Tables 3 and 4).

Comparison of patency rates of the grafts with stage I, II, and III vessel outflow are presented in Tables 5, 6, and 7. The accumulated patency rate in 23 grafts with stage III outflow, similar to patients with isolated popliteal segments, was 90% with two early occlusions and none late. Forty-seven grafts with stage I outflow, comparable to two-three vessel outflow, had an accumulated 4-year patency rate of 75% with five early occlusions and four late failures.

All grafts extended from the common femoral artery to the proximal or the distal popliteal segment. In Tables 8 and 9 the effect of length (and knee joint crossing) are evaluated. Immediate success rates were similar, but between 2 months and 5 years, five more grafts occluded in those below the knee than in those above the knee.

TABLE 1. *Outflow Tract in 123 Femoropopliteal Grafts*

System I			System II (Morton)[14]		
Outflow Grade	No. of Grafts	%	Outflow Grade	No. of Grafts	%
3 vessel	57	45	I	53	43
2 vessel	36	29	II	43	34
1 vessel	13	10			
	30	24	III	27	21
none*	17	13			

* Isolated Popliteal Segment.

Gangrene was the operative indication for vascular reconstruction in 52 (46%) of the 123 grafts performed in this series. Diabetes was present in 27 (49% of the patients with gangrene) and all five operative deaths occurred in this group. There were four early and three late failures, all resulting in major amputations. One patient required amputation with a patent graft having not healed after 9 months. The remaining 34 grafts (61%) available for follow-up resulted in preservation of the extremity with 23 having minor amputations which healed.

Discussion

The reason for failure of femoropopliteal grafts is often difficult to determine. The fact that early failures can frequently be corrected[7] implicates technical errors and, indeed, Darling[6] believes that graft failure in most instances is due to technical errors. In this study an attempt was made to delineate the presence of technical errors by intraoperative arteriograms as well as flow measurements. Similarly, pressure measurements were made simultaneously in the common femoral artery and distal end of the graft to rule out the presence of a gradient. However, early graft failures occurred even when these studies were normal.

Analysis of the 23 failures in this study allows several deductions. Three late graft failures resulted from evident progression of aorto-iliac disease. Two of these failures resulted in amputations and one patient was

TABLE 2. *Analysis of 115 Femoropopliteal Vein Grafts (Life Table Method)*[16]

Interval	No. of Grafts at Risk	No. Patent	No. Occluded	No. not observed Throughout Interval Due to		Failure Rate in Interval %	Patency Rate in Interval %	Accumulated Patency Rate %
				Death or Amputation	Time			
0–30 days	115	106	9	6	0	8.0	91.9	92
2–12 mo.	100	89	11	5	27	13.0	86.9	80
13–24 mo.	55	54	1	6	6	2.0	97.9	78
25–36 mo.	41	40	1	2	11	2.9	97.1	75
37–48 mo.	24	24	0	2	10	0.0	100	75
49–60 mo.	9	8	1	0	6	16.7	83.3	62
61–72 mo.	2	2	0	0	2	0.0	100	62

TABLE 3. *Analysis of 45 Femoropopliteal Vein Grafts for Claudication (Life Table Method)*[16]

Interval	No. of Grafts at Risk	No. Patent	No. Occluded	No. not observed Throughout Interval Due to		Failure Rate in Interval %	Patency Rate in Interval %	Accumulat Patency Ra %
				Death or Amputation	Time			
0–30 days	45	42	3	0	0	6.7	93.3	93
2–12 mo.	42	35	7	1	13	20.0	80.0	74
13–24 mo.	19	19	0	1	3	0.0	100	74
25–36 mo.	15	15	0	1	2	0.0	100	74
37–48 mo.	10	10	0	1	5	0.0	100	74
49–60 mo.	4	4	0	0	4	0.0	100	74

TABLE 4. *Analysis of 67 Femoropopliteal Vein Grafts for Rest Pain and Gangrene (Life Table Method)*[16]

Interval	No. of Grafts at Risk	No. Patent	No. Occluded	No. not observed Throughout Interval Due to		Failure Rate in Interval %	Patency Rate in Interval %	Accumulat Patency Ra %
				Death or Amputation	Time			
0–30 days	67	61	6	6	0	9.4	90.6	91
2–12 mo.	55	51	4	4	14	8.7	91.3	83
13–24 mo.	33	32	1	5	3	3.4	96.5	80
25–36 mo.	23	23	0	1	9	0.0	100	80
37–48 mo.	12	12	0	1	5	0.0	100	80
49–60 mo.	5	4	1	0	2	22.2	77.7	62
61–72 mo.	2	2	0	0	2	0.0	100	62

TABLE 5. *Analysis of 47 Femoropopliteal Vein Grafts With Grade I Outflow (Life Table Method)*[16]

Interval	No. of Grafts at Risk	No. Patent	No. Occluded	No. not observed Throughout Interval Due to		Failure Rate in Interval %	Patency Rate in Interval %	Accumulat Patency Ra %
				Death or Amputation	Time			
0–30 days	47	42	5	1	0	10.8	89.2	89
2–12 mo.	41	38	3	1	9	8.5	91.5	81
13–24 mo.	28	28	0	1	2	0.0	100	81
25–36 mo.	24	23	1	2	6	5.0	95.0	76
37–48 mo.	13	13	0	2	5	0.0	100	76
49–60 mo.	6	6	0	0	6	0.0	100	76

TABLE 6. *Analysis of 45 Femoropopliteal Grafts With Grade II Outflow (Life Table Method)*[16]

Interval	No. of Grafts at Risk	No. Patent	No. Occluded	No. not observed Throughout Interval Due to		Failure Rate in Interval %	Patency Rate in Interval %	Accumulat Patency Ra %
				Death or Amputation	Time			
0–30 days	45	43	2	2	0	4.5	95.4	95
2–12 mo.	41	33	8	3	10	23.2	76.8	73
13–24 mo.	19	18	1	3	3	6.3	93.7	68
25–36 mo.	12	12	0	0	2	0.0	100	68
37–48 mo.	9	9	0	0	4	0.0	100	68
49–60 mo.	3	2	1	0	0	33.3	66.6	45
61–72 mo.	2	2	0	0	2	0.0	100	45

TABLE 7. *Analysis of 23 Femoropopliteal Vein Grafts With Grade III Outflow (Life Table Method)*[16]

Interval	No. of Grafts at Risk	No. Patent	No. Occluded	No. not observed Throughout Interval Due to		Failure Rate in Interval %	Patency Rate in Interval %	Accumulated Patency Rate %
				Death or Amputation	Time			
0–30 days	23	21	2	3	0	9.3	90.7	90
2–12 mo.	18	18	0	1	9	0.0	100	90
13–24 mo.	8	8	0	2	1	0.0	100	90
25–36 mo.	5	5	0	0	3	0.0	100	90
37–48 mo.	2	2	0	0	1	0.0	100	90

TABLE 8. *Analysis of 59 Femoropopliteal Above Knee Vein Grafts (Life Table Method)*[16]

Interval	No. of Grafts at Risk	No. Patent	No. Occluded	No. not observed Throughout Interval Due to		Failure Rate in Interval %	Patency Rate in Interval %	Accumulated Patency Rate %
				Death or Amputation	Time			
0–30 days	59	54	5	4	0	8.8	91.2	91
2–12 mo.	50	47	3	2	14	7.1	92.8	84
13–24 mo.	30	0	0	3	3	0.0	100	84
25–36 mo.	23	22	1	1	7	5.3	94.7	79
37–48 mo.	14	14	0	2	4	0.0	100	79
49–60 mo.	6	6	0	0	5	0.0	100	79
61–72 mo.	1	1	0	0	1	0.0	100	79

TABLE 9. *Analysis of 56 Femoropopliteal Below The Knee Vein Grafts (Life Table Method)*[16]

Interval	No. of Grafts at Risk	No. Patent	No. Occluded	No. not observed Throughout Interval Due to		Failure Rate in Interval %	Patency Rate in Interval %	Accumulated Patency Rate %
				Death or Amputation	Time			
0–30 days	56	52	4	2	0	7.3	92.7	93
2–12 mo.	50	42	8	3	13	19.0	80.9	75
13–24 mo.	25	24	1	3	3	4.5	95.4	71
25–36 mo.	18	18	0	0	4	0.0	100	71
37–48 mo.	10	10	0	0	6	0.0	100	71
49–60 mo.	3	2	1	0	1	40.0	60.0	42
61–72 mo.	1	1	0	0	1	0.0	100	42

regrafted following a femoro-femoral graft. At the time of regrafting a severe stenosis in the opposite common femoral artery was opened with a patch graft in order to preserve the patency of a femoropopliteal graft in that leg. Closer observation of the inflow tract and appropriate therapy when indicated could have prevented the failure of these grafts.

Six other failures were possibly related to the vein. One graft was performed with a vein greater than 8 mm. in diameter and failed at 2 months. Darling[6] has indicated that veins greater than 8 mm. in diameter are too large to function satisfactorily. Another graft was performed with a saphenous vein less than 3 mm. in diameter and failed immediately. This patient was subsequently regrafted bilaterally with arm veins with good results. Four other patients were grafted with veins requiring extensive reconstruction resulting in three immediate failures and one at 7 months. Veins that are too large, too small or require extensive reconstruction result in poor patency rates.

Of the remaining grafts which failed, two were operative failures in which no flow could be established in the popliteal artery and the grafts were extended to distal tibial vessels, one successfully. No reason for failure could be incriminated in three other grafts which failed immediately and eight which failed after 6 months. Although not documented in this series, there is ample evidence to suggest that progressive segmental stenosis leading to thrombosis can occur in relationship to valves[2,3,9,13] or perhaps at previous sites of venous disease (phlebitis). One of our patients has had acute graft thrombosis on three occasions 1 year apart and on each occasion flow was restored by balloon catheter thrombectomy.

Our observations support those of others[6] in indicating that graft patency is not dependent on the status of the outflow tract. We have recently seen two patent grafts with total occlusion of the popliteal artery immediately distal to the anastomosis.

The value of femoropopliteal reconstruction in preserving gangrenous extremities has been well documented[8,19] (Table 4). We believe that the extremity with rest pain is nearly as threatened as the one with frank gangrene and do not share the reservations of Stoney and associates [17] about vascular reconstruction for limb salvage in these patients.

The higher late failure rate for grafts extending to the distal popliteal artery has not been a consistent observation.[6,8]

We believe that the best method of femoropopliteal reconstruction is with the autogenous saphenous vein. The strength of this conviction is supported by the fact that endarterectomy and synthetic bypass have not been used in this interval. On the other hand it is apparent that a significant number of grafts fail, both early and late, for technical reasons which are frequently related to the vein itself. Therefore, a search for other methods of arterial reconstruction remains logical. One such method which shows promise has been described by Sparks and has the advantage of providing a uniform graft with an autogenous flow surface.[15]

Summary

The patency rates of 123 femoropopliteal vein grafts have been presented. Patency rates were evaluated with regard to the symptomatic indications for grafting, stage of the disease in the outflow tract, and the length of the graft. An analysis of the causes of the failures is presented.

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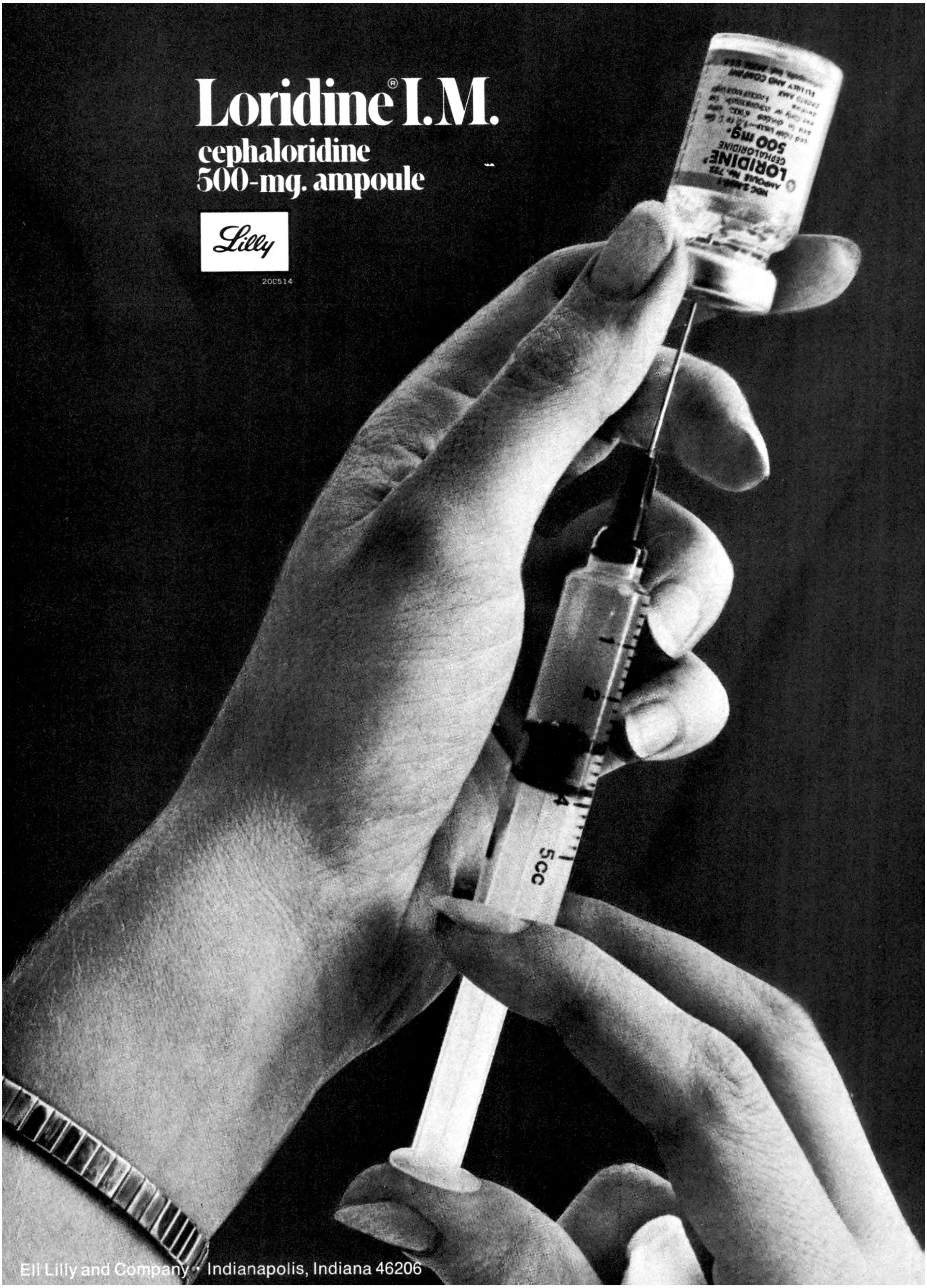

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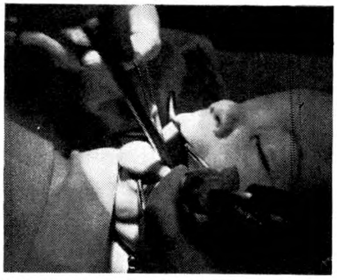

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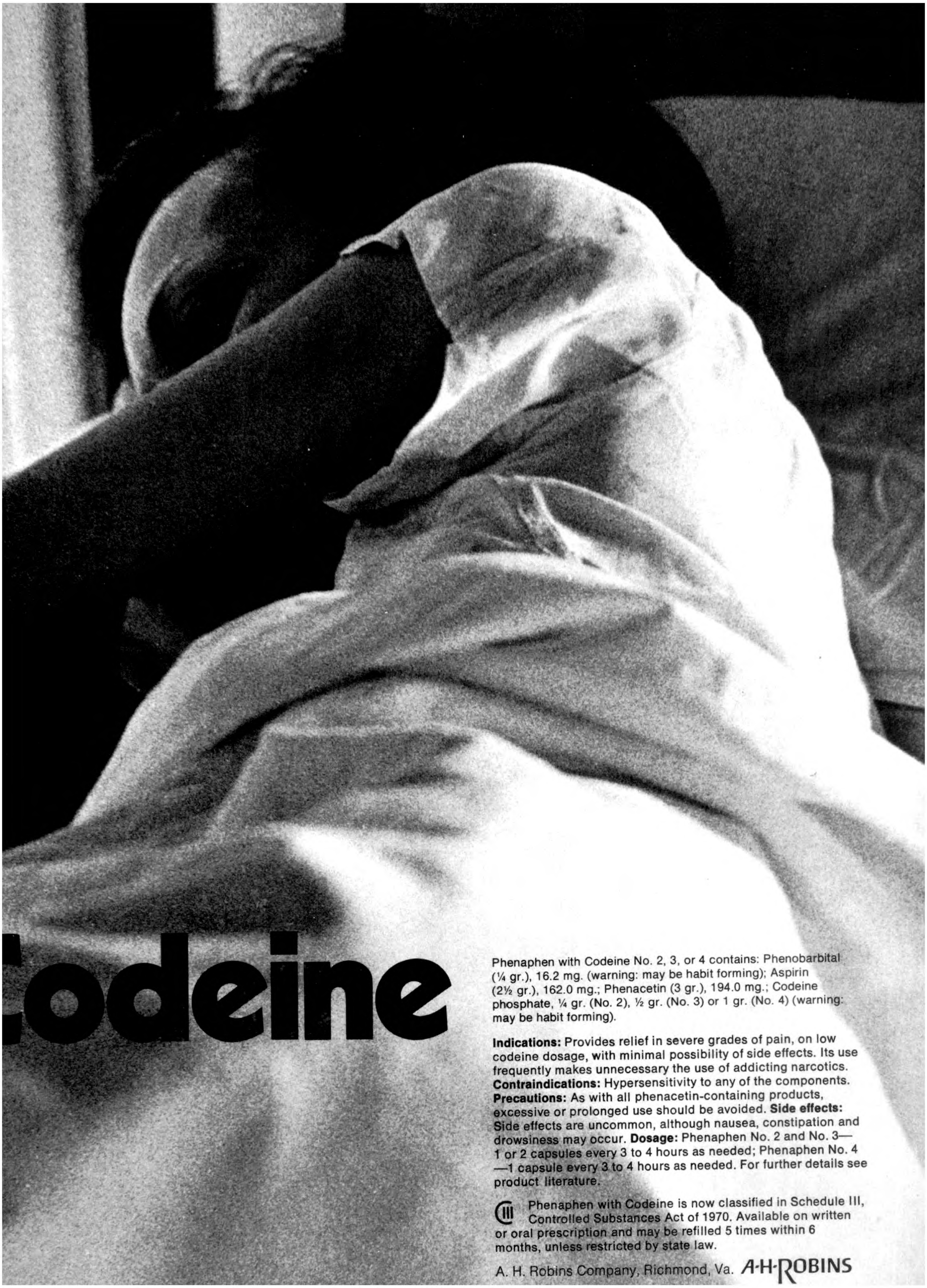

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LEIOMYOSARCOMA of the inferior vena cava is a rare tumor that has led to reported surgical intervention in only nine patients. This paper presents another case in which aggressive surgical treatment afforded excellent palliation. Moreover, it is by far the most extensive palliative surgical procedure that has been reported for leiomyosarcoma of the inferior vena cava.

Case Report

A 58-year-old housewife entered the University of Chicago Hospitals for the first time in July, 1967, with gastrointestinal bleeding and abdominal pain. Her pertinent medical history began with right lower quadrant and right lumbar pain which led to negative laparotomy at another hospital in January, 1963. Subsequently she developed a right upper quadrant mass which at laparotomy in April, 1964, was found to be leiomyosarcoma arising from the inferior vena cava. The tumor was amputated from the vena cava, but the vena cava itself was not disrupted. A third laparotomy was performed in April, 1965, for recurrence of the right upper quadrant abdominal mass. The locally recurrent tumor had invaded the duodenum and pancreas; no attempt at palliative resection was made. In January, 1967, she began to have frequent episodes of gastrointestinal bleeding which required at least 20 hospitalizations and transfusion with 150 units of whole blood during a 6-month period. She required narcotics for control of abdominal pain.

At the time of her first admission to The University of Chicago Hospitals, she was well developed, afebrile, normotensive, weighed 60 Kg. (height 160 cm.) and had a visible mass that filled the right upper abdominal quadrant. The feces was strongly positive for occult blood; hematocrit was 24% and total serum proteins were 5.3 gm./100 ml. Chest X-ray was normal. Barium examination of the stomach and duodenum demonstrated compression of the antrum and invasion of the first and second parts of the duodenum. An intravenous pyelogram was normal except for downward displacement of the right kidney. An aortogram with injections of contrast material into the superior mesenteric artery demonstrated a right mid-abdominal mass that elevated the main hepatic artery, displaced several branches of the superior mesenteric artery anteriorly and depressed the right renal artery (Fig. 1 and 2). Inferior vena cavagram revealed anterior and medial displacement of the mid-inferior vena cava and almost total occlusion of its lumen by an intrinsic mass; there were large lumbar venous collaterals (Fig. 3).

Laparotomy was performed in August, 1967. The right mid-abdomen was filled with a firm well-defined tumor mass, 15 cm. in diameter, which arose from the right side of the inferior vena cava adjacent to the renal vein. The cephalad part of the tumor invaded the anterior surface of the head of the pancreas and the proximal duodenum. The portal vein, superior mesenteric artery and celiac axis were not invaded; there were no apparent regional lymph node metastases. A solitary 3 cm. mass was present in the lateral segment of the left hepatic lobe.

The tumor mass was resected in continuity with the distal half of the stomach, the entire duodenum, the proximal half of the pancreas, a 12 cm. segment of proximal jejunum and a 6 cm. segment of the inferior vena cava that included a one cm. segment of the right renal vein. The stumps of the remaining inferior vena cava were oversewn and the residual right renal vein was anastomosed end to side to the inferior remnant of vena cava. The lateral segment of the left hepatic lobe was resected. Gastrointestinal continuity was reestablished by end to end pancreatico jejunostomy, end to side choledochojejunostomy and end to side gastrojejunostomy in that order. Her postoperative course was complicated by subphrenic abscess and pneumonia. An intravenous pyelogram prior to discharge was normal. She resumed normal activity and was free from edema of the lower extremities.

In December, 1968, a routine search for metastases which included chest X-ray, radiographic bone survey and technetium liver scan revealed a single 5 cm. defect in the posterior-most aspect of the right hepatic lobe. The hepatic metastasis was resected through the bed of the right tenth rib. Her postoperative course was uneventful and she returned to full activity.

She was re-evaluated again in December, 1969, still asymptomatic and active. Physical examination revealed two 1–2 cm. subcutaneous masses over the right scapula and the spinous process of the tenth thoracic vertebra. At the time of biopsy the mass over the spinous process was noted to arise from the paraspinous muscles. Microscopic examination confirmed the di-

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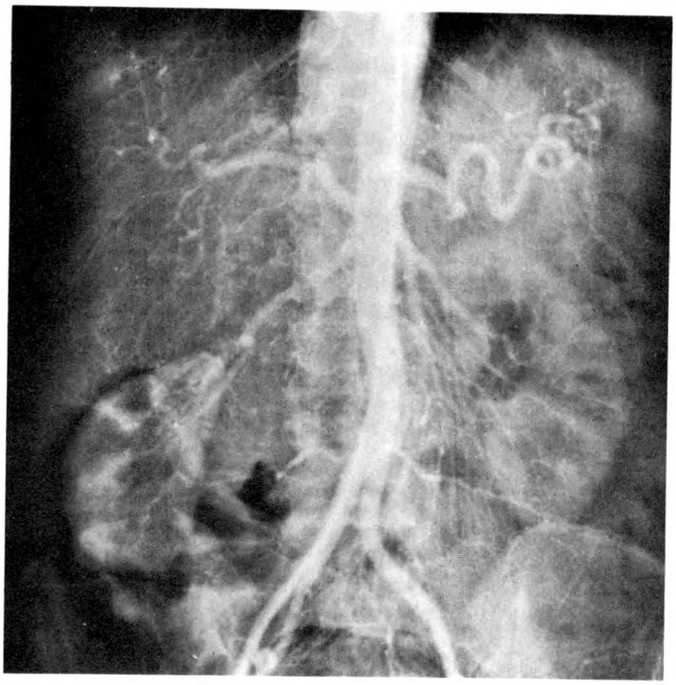

FIG. 1. Aortogram shows elevation of the proximal hepatic artery and depression of the right kidney.

agnoses of recurrent leiomyosarcoma. In addition a new filling defect in the right hepatic lobe was detected by liver scan.

She was referred to the National Cancer Institute to be considered for immunotherapy which was begun in March, 1970. Despite those efforts she developed further metastatic involvement and required decompressive laminectomy for relief of severe sciatic pain in July, 1970. She had widespread metastases when she died in November, 1971.

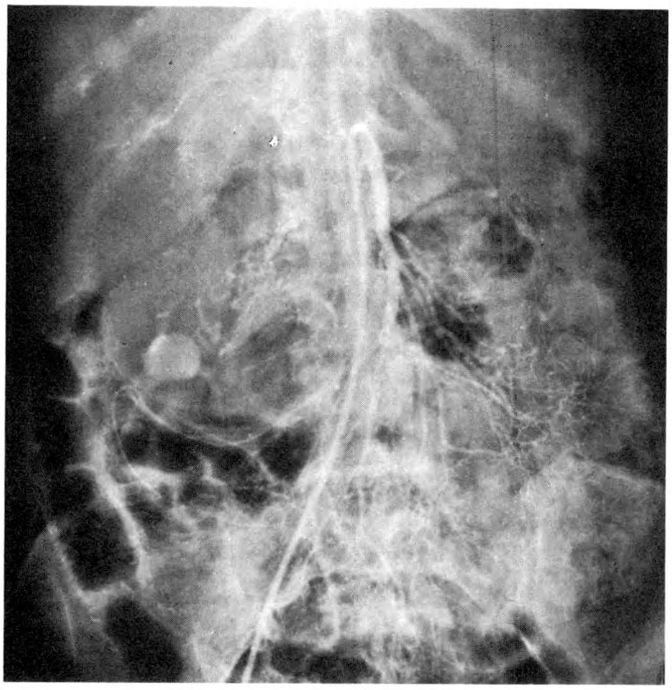

FIG. 2. Selective superior mesenteric arteriogram outlines a large mass in the right upper quadrant of the abdomen.

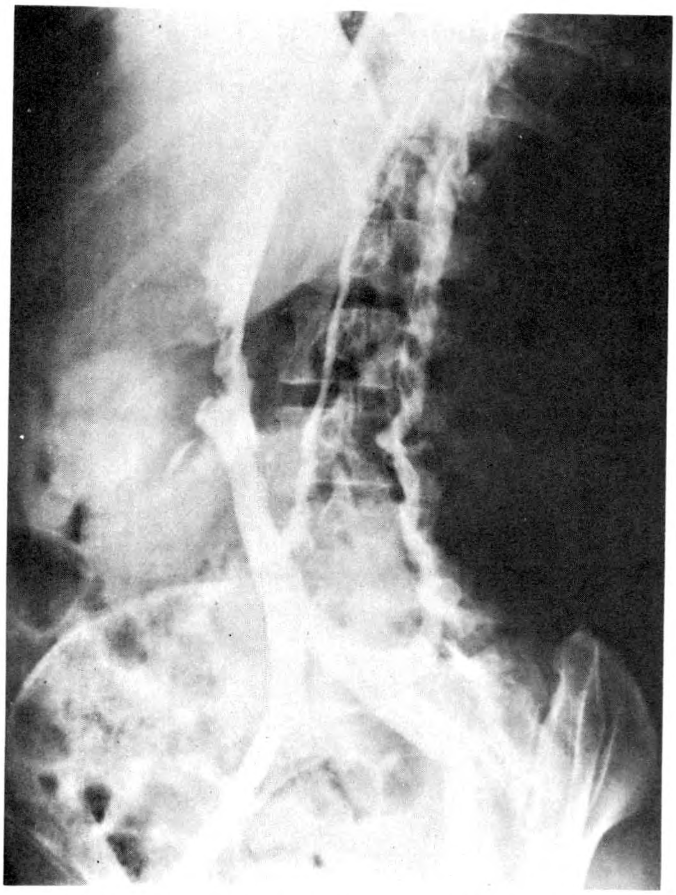

FIG. 3. Inferior vena cavagram shows almost total occlusion of the IVC by tumor at the level of the second lumbar vertebra. Ascending lumbar veins are greatly dilated bilaterally.

Discussion

Leiomyosarcoma of the inferior vena cava is a moderately slow growing tumor that occurs almost exclusively in women and affects all age groups (Table 1). Most of the reported cases have been diagnosed only at autopsy, but at least ten cases have led to curative or palliative resection. The tumor spreads by direct invasion and by widespread metastases, although metastases may not become manifest until several years after resection of the primary tumor.

The most common presenting complaint is right upper quadrant abdominal pain which was frequently thought to be due to biliary disease. An abdominal mass was palpable in half of the patients. Edema of the lower extremities was infrequent; development of collateral venous channels apparently kept pace with the relatively slow growing intravascular tumors.

Our patient had been symptomatic for 4 years when we first saw her. Her diagnosis had been established for 3 years. It is unfortunate that a curative resection was not attempted during laparotomy in 1963 or 1964. In addition to her large tumor, she presented in 1967 with frequent life-threatening hemorrhage secondary to invasion of the stomach and duodenum by tumor. A major

TABLE 1. *Reported Cases of Surgical Resection for Leiomyosarcoma of the Inferior Vena Cava*

Author	Year Reported	Age	Sex	Presenting Symptoms	Procedure	Follow-up
Melchior	1928	24	Female	Back pain	Resection IVC	Died 17 days after operation
Cope & Hunt	1954	33	Female	Back pain	Resection IVC	Postoperative radiation; recurrence at 16 months; resected but recurred after 12 months; treated with implants
Allan	1964	65	Male	Abdominal pain, weight loss, fever	Resection of 2400 gm. tumor mass and anterior wall of IVC	Recurred in 5 months; treated with palliative gastrojejunostomy and radiation; asymptomatic and no palpable mass 1 year later
Caplan	1964	72	Female	Right abdominal and back pain, weight loss	Suprarenal IVC and tumor resected	Free of disease at 7 weeks, no additional follow up
Staley	1967	65	Female	Abdominal mass	Resection of mass and anterior wall IVC	Metastases and death after 1 year
Hopson	1967	72	Female	RUQ abdominal mass	Resection of IVC and mass	Free of disease 7 months
Gariepy	1967	47	Female	RUQ abdominal pain and mass	Resection of IVC and mass	Symptom free for 4 years, then died from recurrent tumor and GI bleeding a year later
Jurayj	1970	66	Female	RLQ abdominal pain and mass	Resection of infra renal IVC and 700 gm. mass	Died of metastases at 8 months
Dube	1971	61	Female	RUQ abdominal pain	Resection of IVC and mass	Free of recurrence at 9 months
Stuart	1972	58	Female	RUQ abdominal pain and mass; upper GI bleeding	Resection of IVC and mass including pancreas, duodenum and stomach	Died 4 years after major palliative resection; extensive metastases at that time.

resection of her tumor including the invaded stomach, duodenum, pancreas and inferior vena cava was accomplished; no visible or palpable tumor remained. Her pain and hemorrhage were controlled successfully. Except for several short periods of hospitalization she was able to lead a relatively normal life for almost 3 years after major resection. She then entered the pre-terminal phase of her metastatic disease, but local intra-abdominal recurrence was still not evident when she died, more than 4 years after palliative resection. The case presented by Gariepy[5] is also an example of late invasion of the stomach and massive hemorrhage that occurred 4 years after resection of the primary tumor.

In our patient, the right renal vein was anastomosed to the caudad segment of the inferior vena cava. Longstanding obstruction of her inferior vena cava had led to the development of extensive venous collaterals, and pressure in the caudad vena cava was less than 10 cm. of water. Postoperative pyelograms were normal. Sufficient venous collaterals had also developed in the patient presented by Caplan to allow resection of the suprarenal inferior vena cava without causing impairment of renal function.[2]

Follow-up of the ten reported cases that led to operation has ranged from 2 weeks to 4 years. Of the five patients who were followed for more than a year, the tumor eventually recurred in four. Even though they were not cured, they were afforded effective palliation for as long as 4 years. In the case that we have reported the patient's tumor was present for 8 years. Complete resection was not attempted until 3 years after the diagnostic laparotomy and partial resection.

Summary

The tenth patient with a surgically resected leiomyosarcoma of the inferior vena cava is presented. The moderately slow growth of these tumors is emphasized, and an aggressive surgical approach is encouraged. *En bloc* resection of this patient's tumor, together with the distal stomach, duodenum, pancreas and inferior vena cava controlled the local tumor and afforded excellent palliation for more than 3 years.

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Experiences with the Use of Intracholedochal Heparinized Saline for the Treatment of Retained Common Duct Stones

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WE RECENTLY REPORTED a case of retained common duct stones treated with a continuous infusion of heparinized saline through a T-tube with disappearance of the stones on follow-up cholangiograms.[2] That patient was initially treated with saline alone for a period of 7 days at which time a cholangiogram demonstrated the continued presence of at least three stones. In a dose of 25,000 u every 8 hours heparin was added to the continuous saline infusion at that time and a cholangiogram repeated 5 days later was of poor quality but seemed to demonstrate disappearance of the stones. An additional week of heparinized saline infusions were given with follow-up cholangiographic evidence of stone disappearance. Since that report five additional patients have been successfully treated by this means and are the subject of this report.

Case Report

Case 1. Patient V. T. underwent cholecystectomy and common duct exploration at Hitchcock Clinic in Hanover, N. H. Three postoperative cholangiograms demonstrated the retention of a large stone in the lower portion of the common bile duct. Figures 1 & 2 show evidence of the stone on cholangiography on 6–11–71 and 7–16–71. The patient was readmitted and treated with a heparinized saline irrigation drip continuously through the T-tube at a dose of 25,000 units of heparin per 250 cc. of saline every 6 hours. The patient had mild symptoms of cholangitis for the first 3 days of the choledochal drip which subsided spontaneously over the last 3 days of irrigation. A repeat cholangiogram (Fig. 3) on 7-28-71 demonstrated disappearance of the stone at which time the T-tube was clamped. This was well tolerated by the patient and the tube was removed 1 week later.

Case 2. A 69-year-old man was operated upon for obstructive jaundice and intestinal angina at Auburn, N. Y. Cholecystectomy and common duct exploration was performed with removal of common duct stones and a vein patch graft was applied to the superior mesenteric artery. Postoperative cholangiograms showed the presence of a retained stone on 7-16-71 (Fig. 4). The patient was a poor candidate for re-exploration and was followed as an out-patient. A repeat cholangiogram on 10-1-71 again demonstrated the presence of a large stone in the lower end of the common bile duct (Fig. 5). He was readmitted and given an infusion of 15,000 u of heparin in 250 cc. of saline every 6 hours through the T-tube. Approximately 20 hours after the start of the infusion the patient had a severe episode of colicky pain which lasted 20 minutes. Occasional intermittent episodes of pain lasting a minute or so recurred over the next 2 days and following that no further pain was noted. A T-tube cholangiogram was carried out which demonstrated a normal biliary tract. Figure 6 demonstrates a repeat cholangiogram taken 11-2-71 showing a reduction in size of the common bile duct and disappearance of the stones. The T-tube was subsequently removed and the patient has done well.

Case 3. M. K. was operated upon at the Kings County Hospital for jaundice and a sub-acute cholecystitis. A cholecystectomy and common duct exploration revealed common duct stones. He did well postoperatively but a T-tube cholangiogram performed on 7-19-71 (Fig. 7) demonstrated the presence of a stone in the lower portion of the common bile duct and failure of the dye to pass into the duodenum. The patient was treated with continued drainage of the T-tube and a repeat cholangiogram on 7-27-71 (Fig. 8) again demonstrated a retained common duct stone blocking exit of dye from the common bile duct into the duodenum. The patient was then started on 25,000 u of heparin in 250 cc. of saline as a continual drip every 8 hours through the T-tube. He experienced no episodes of cholangitis and tolerated the drip well. A repeat cholangiogram was made on 8-2-71 and demonstrated disappearance of the stone from the common bile duct and free entrance of the dye into the duodenum (Fig. 9). At this point the T-tube was removed and the patient's remaining postoperative course was uneventful.

Case 4. E. R. was operated upon at the Kings County Hospital undergoing cholecystectomy and common duct exploration for cholecystitis and jaundice. Her postoperative course was uneventful and on 12-30-71 a cholangiogram was performed. This demonstrated a failure of dye to enter the duodenum (Fig. 10) and was interpreted as a stone retained in the lower portion of the

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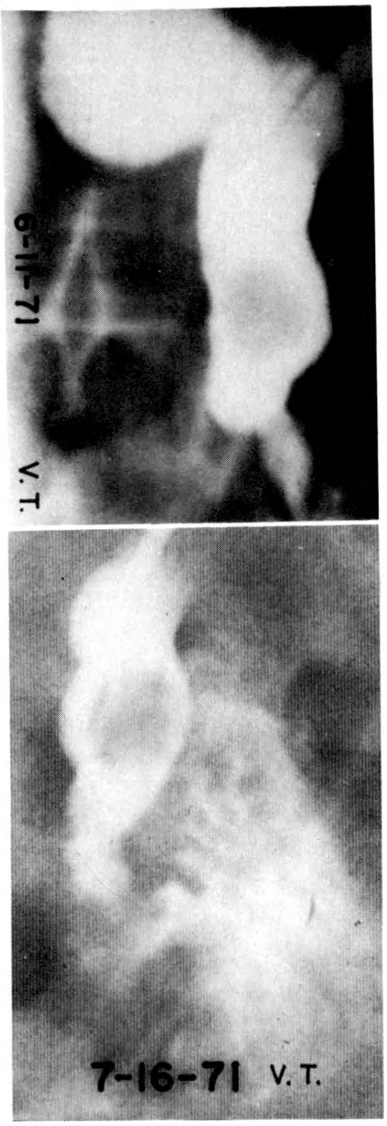


FIG. 1 and 2. Case 1—Large retained common duct stone.

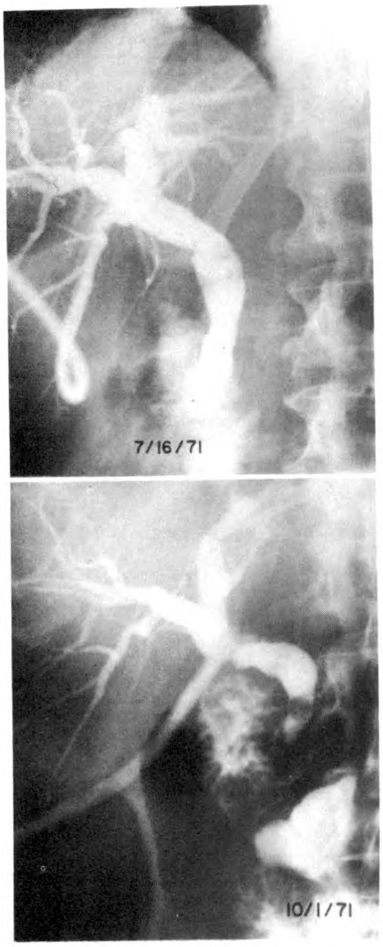


FIG. 4 and 5. Case 2.—Large retained stone at lower end of common bile duct.

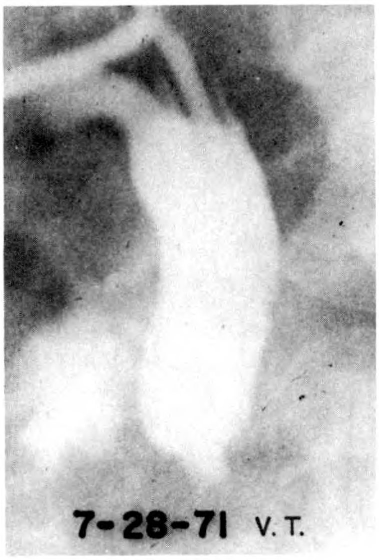


FIG. 3. Case 1—After heparin treatment the stone is gone.

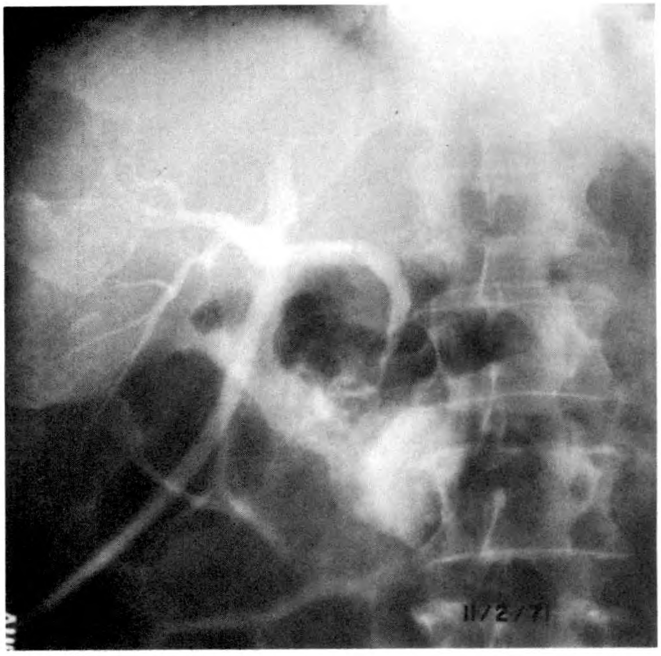


FIG. 6. Case 2—Demonstrating normal common duct without stones.

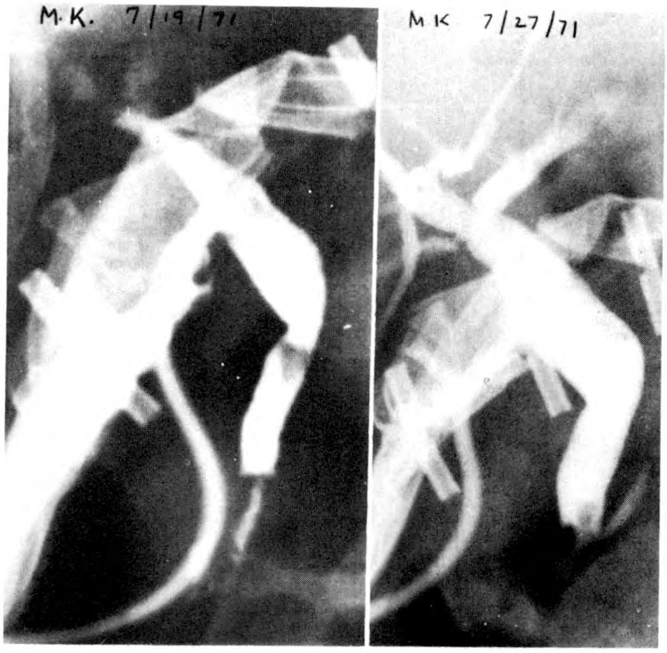


FIG. 7 and 8. Case 3—Retained common duct stone with failure of passage of dye into duodenum.

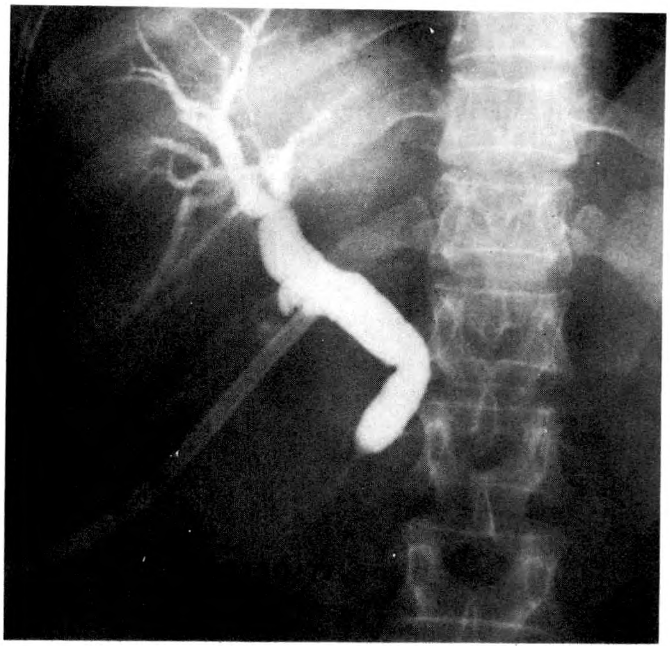


FIG. 10. Case 4—Obstruction of flow of dye into duodenum with configuration of stone in lower end of duct.

duct because of the configuration of the lower end of the bile duct with a sharp cut-off. The patient was started immediately on a heparinized saline drip using 25,000 u of heparin in 250 cc. of saline every 8 hours. The patient experienced no cholangitis or pain and tolerated the drip without difficulty. A repeat cholangiogram was performed on 1-6-72 (Fig. 11) and demonstrated free passage of dye into the duodenum without evidence of obstruction and no stone could be demonstrated. The T-tube was removed and the patient's remaining course was uneventful.

Case 5. An obese woman was operated upon at St. John's Hospital in Brooklyn for acute cholecystitis and jaundice on 12-17-71. Common duct stones were found and a T-tube was left in place postoperatively. A cholangiogram (Fig. 12) on 12-22-71 demonstrated retained common duct stones. On 12-25-71 the patient eviscerated and was reoperated upon as an emergency at which time a re-exploration of the common bile duct was performed revealing three additional stones. A T-tube was again left in place, the incision was closed and on 12-30-72 repeat cholangiogram demonstrated failure of passage of dye into the duodenum. The patient was treated with bile salts and magnesium sulfate by mouth and several irrigations of the T-tube with ether and nitrites. On 1-11-72 a repeat cholangiogram (Fig. 13) again demonstrated retained common duct stones. Because of the previous two operations it was felt unwise to re-explore the patient again at this time

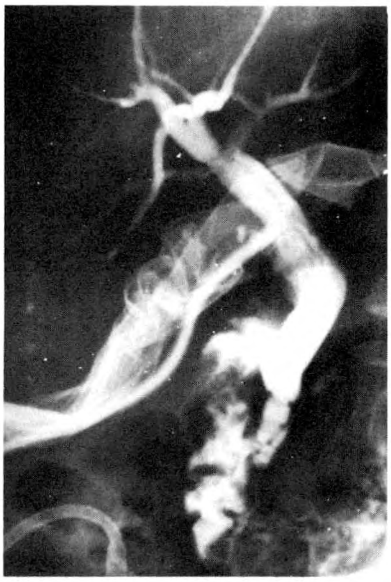


FIG. 9. Case 3—Demonstrating free passage of dye into duodenum and no retained stones (8/2/71).

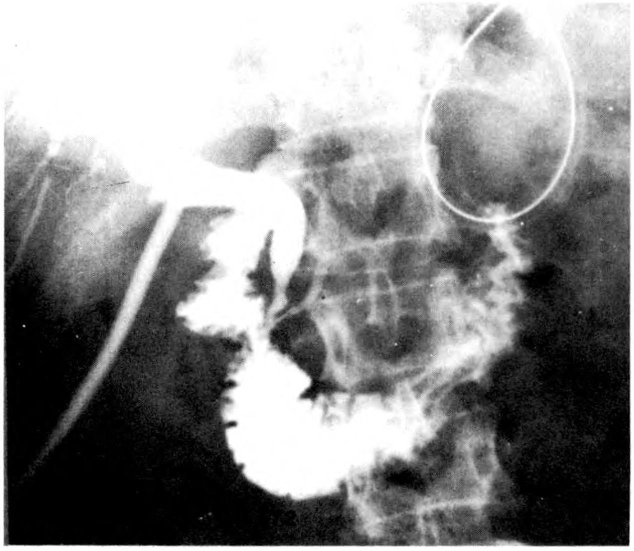


FIG. 11. Case 4—Normal common duct.

FIG. 12. Case 5—Demonstration of retained stones in common bile duct.

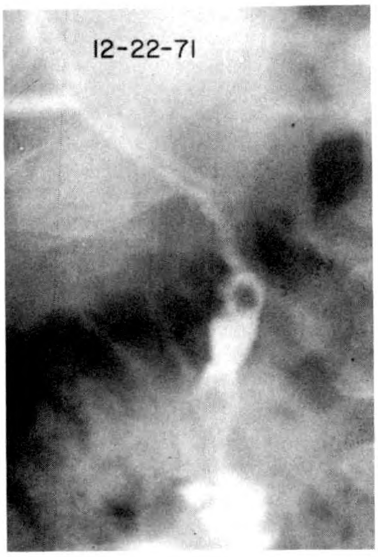
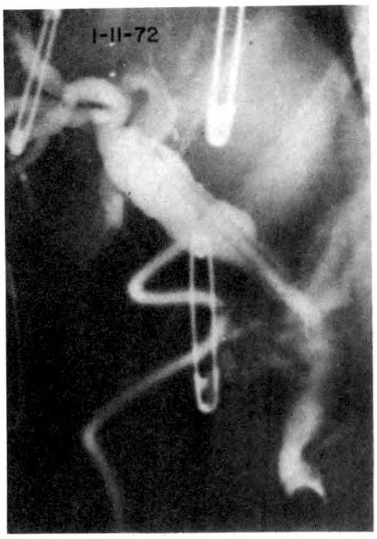


FIG. 13. Case 5—After treatment with ether irrigations and nitrites—retained stones are demonstrated.



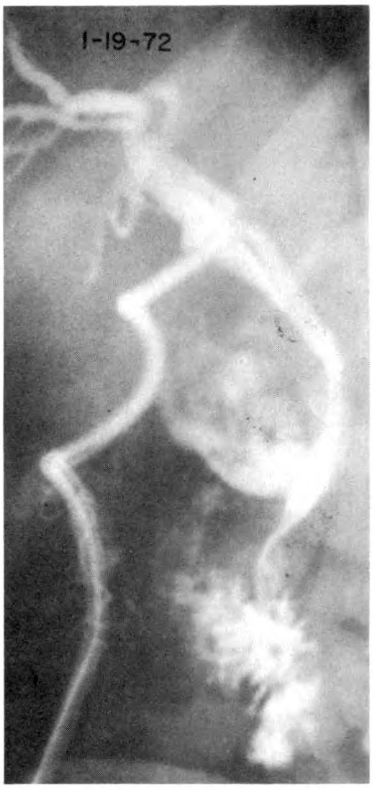
and heparinized saline irrigations were begun through the T-tube using 15,000-20,000 u of heparin in 250 cc. of saline every 8 hours as a continual slow drip. The patient experienced no discomfort or cholangitis from the treatment and on 1-19-72 a cholangiogram (Fig. 14) demonstrated complete patency of the biliary system, disappearance of the stone, and a rapid entrance of the dye into the duodenum. The T-tube was subsequently removed and the patient's course was then uneventful.

Discussion

We hypothesize on the basis of our previous work[2,3] that heparinized saline would be a useful adjunct in the irrigation of the common bile duct in which precipitation of sediment was a problem. We were pleased to publish a successfully treated instance in which retained common duct stones disappeared by use of this treatment. At that time we encouraged other surgeons to attempt the treatment when indicated in order to test its efficacy and have thereby accumulated the subsequent five case reports.

The theory is based on increasing the suspension stability of bile by the addition of a highly negatively charged ion (heparin). We have demonstrated marked increases in negative zeta potential of a standard particle electrophoresed in bile containing heparin.[3] This indicated that the bile salt lecithin cholesterol micelles might be readily dispersed in solutions of this type. It is possible that the development of a gallstone with a calcified surface would tend to militate against dissolution merely on the basis of alteration of suspension stability of the solution in which the gallstone is placed. However, if the polar groups on the surface of the stone are positively charged and oriented toward the solution some dispersion may then occur in the presence of large quantities of negatively charged ions leading to softening or fragmentation of the stone. We do not feel that the irrigations alone are responsible for the success of the treatment since in the original case saline without heparin failed to remove the stones and in the last case reported in this paper—irrigations with ether and nitrites failed to alter the configuration of the retained stones. Unfortunately the other patients in the cases reported were not initially treated with a control solution in order to further test that hypothesis. In addition it is unlikely that the stones are passed in their original form since the large size of the stones as noted on the cholan-

FIG. 14. Case 5—After heparinized saline irrigations—duct is normal.



giogram of the first two reported cases would heavily militate against spontaneous passage. It is more likely that fragmentation of the stone is occurring with the heparin drip and the smaller particles are then spontaneously passed. Another possibility may be a direct effect of heparin on the sphincter at the lower end of the common bile duct with either reduction in postoperative inflammation or sphincter relaxation being responsible in part for the stone passage. Once again, there would have to be some alterations in the size or configuration of the stones in order to explain the disappearance of the large stones noted in the first two cases.

The six cases so far reported represent an addition to the repertoire of treatment for retained common duct stones with a T-tube in place. Unfortunately destruction of heparin prevents its oral use and parenteral heparin produces alterations in blood clotting which would prohibit its use by that route for dissolution of gallstones. We have no evidence at the present time of excretion of heparin via the bile.

Summary

Five additionad cases of retained common duct stones which disappeared after irrigation of a common duct with heparinized saline are presented. Cholangiographic evidence is presented which indicates that this procedure represents an important addition to the treatment of retained common duct stones.

Addendum

At the present time we have accumulated 15 successful cases and four failures with this treatment for retained common duct stones.

Acknowledgment

We are indebted to Drs. Weismann, Buffington and Coppola for the use of cholangiograms reported in this paper.

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Chylothorax:

Indications for Surgery

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THE MANAGEMENT OF chylothorax can be extremely difficult because of the tremendous diversity seen in its magnitude and etiology. Moreover personal experience is usually limited by its infrequent occurrence, so that unrecognized deterioration can occur rapidly due to the devastating metabolic effects of excessive chyle loss.

For years this entity was associated with a mortality rate of almost 50 per cent. Only in the past quarter-century have survival statistics improved. This is directly attributable to the introduction of successful transthoracic ligation of the thoracic duct by Lampson[2] in 1946. This has proven to be a sound surgical approach to the management of chylothorax. By no means, however, should this imply that all patients should undergo ductal ligation. It is often unnecessary and at times even contraindicated. Herein lies the crux to the treatment of this entity. A familiarity with the indications for operation in chylothorax is essential for most effective management.

Recent experience with two cases of widely differing magnitude has prompted a review of the instances of chylothorax treated at the University of Cincinnati Medical Center during the past 29 years. It is intended in the context of this review to illustrate the dangers of prolonged nonoperative therapy, and to better define the clinical setting in which surgical intervention is indicated.

Anatomy

A surgical approach to the thoracic duct requires a clear understanding of its anatomy. A bilateral structure embryologically, it has the potential of having many varied anatomical patterns. The "standard" pattern is only present about half of the time. Many minor variations occur in lymphatic and lymphaticovenous anastomoses. A rich collateral network exists that permits ligation of the duct at any point throughout its course. Most commonly, the duct originates from the cisterna chyle in the midline at the level of the second lumbar vertebra. It enters the thorax through the aortic hiatus to the right of midline, and is covered by the aorta. In the inferior thorax it lies beneath the mediastinal pleura between the aorta and azygous vein and is covered by the esophagus. It crosses to the left at about the level of the fourth or fifth thoracic vertebra. Here it lies behind the aortic arch and, more superiorly, the left subclavian artery. Having entered the neck it curves ventrally to cross the scalenus anticus muscle and phrenic nerve, and empties into the junction of the left internal jugular and subclavian veins.

A significant point in surgical anatomy is that the duct is essentially always a single structure on the right between the eighth and twelfth thoracic vertebrae. Accordingly a right thoracotomy can be utilized for ductal ligation with confidence in those cases where there are no other factors indicating the side of entry. The appropriate side of approach is obvious in cases of unilateral effusion and in those resulting from initial thoracic surgery.

Clinical Material

Fifteen patients were treated for chylothorax at the University of Cincinnati Medical Center from July 1942 through July 1971. Eight were children under five years

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of age and seven were adults over 21 years of age. Ten were female and five male. Seven cases occurred on the right, five on the left, and three were bilateral. All 15 had at least one thoracentesis revealing typical chylous fluid.

Seven patients had major complications during the period of nonoperative therapy (Table 1), and five patients died.

The number of thoracenteses in each case ranged from one to 34 (Table 2). The highest average volume was seen in the adult trauma group (27,900 cc.) and the lowest in the neonatal idiopathic group (220 cc.).

Seven instances of nontraumatic etiology were encountered (Table 3). Three resulted from compression of the thoracic duct by mediastinal involvement of an underlying disease. One patient had mediastinal tubercular lymphadenopathy, another metastatic thyroid carcinoma, and the third malignant lymphoma. Each patient was treated nonoperatively and eventually died from the primary disease. Three other instances presented idiopathically in the neonatal period and were also treated nonoperatively. Their average total chyle flow was only 220 cc. and all three patients recovered completely. The final nontraumatic instance occurred in a woman with congenital angiomatous transformation of the lymphatic system who declined slowly over a 2-month period with only a minimal but continuous chyle leak. Operation to relieve severe pulmonary-constricting chylofibrosis was unsuccessful and she died intraoperatively.

Eight occurrences resulted from trauma (Table 4). Four occurred in children following cardiovascular surgery. Two of these required reoperation for thoracic duct ligation and all four were cured. One man acquired chylothorax following a left parotidectomy and radical neck dissection for carcinoma of the parotid gland. His chylothorax was voluminous and transthoracic ligation of the thoracic duct was necessary. Another patient developed chylothorax following resection of a thoracic aortic aneurysm, was not reoperated upon, and represents the only death in the traumatic group. Two nonsurgical traumatic cases occurred. The first resulted from a gun shot wound in which the bullet grazed th hepatic dome and crossed the diaphragm to finally lodg in the body of the eleventh thoracic vertebra. After having drained 56,000 cc. of chyle over a 6-week period the leak stopped spontaneously. This case occurred i 1942, prior to Lampson's introduction of thoracic duc ligation. The final traumatic case is presented in detai to illustrate some of the therapeutic difficulties whic can be encountered in the management of chylothorax.

TABLE 2. *Magnitude of Chyle Loss*

Patient Groups		Total Vol. (ml.)	No. Taps
Nontraumatic			
Children			
Idiopathic	3	52–300	1–3
Malignancy	1	3300	11
Adults	3	1100–12,500	2–10
Traumatic			
Children	4	110–1800	1–6
Adults	4	12,000–56,400	4–34

Case Report

Case 14. G.H., a 22-year-old policeman was accidentally throw from his motorcycle on April 13, 1971 resulting in a spinal dislocation between the twelfth thoracic and first lumbar vertebrae The only abnormalities noted on admission were decreased sensation in the distribution of T-12 and L-1 bilaterally and dysesthesia over both lower extremities. Chest x-ray was normal. On th fourth hospital day severe dyspnea was noted. Examination an roentgenography of the chest revealed a large right pleural effusion (Fig. 1). Two chest tubes, 12 mm. in diameter, wer inserted to release 4000 cc. of serosanguineous fluid which assumed a chylous nature by the following day. Sudan stain wa positive for fat.

The patient was given a low fat, high calorie, high protein die and daily albumin infusions. Chyle flow was averaging 2000 cc per day with a consequent fall in serum albumin from 3.8 to 1. Gm./100 ml. and a loss of 30 pounds in body weight. Due to th chyle's gelatinous nature, chest tube obstruction frequently occurred in spite of streptokinase instillation, and tube replacemen was often necessary. On April 26 the patient sustained a pulmonar embolus which necessitated postponing intended thoracic duc ligation.

On April 30 the patient underwent inferior vena cava clippin and thoracic duct ligation. Numerous fresh pleural adhesions an

TABLE 1. *Complications of Nonoperative Therapy (7 Patients)*

Inherent to chylothorax	
Pleural adhesions and fibrosis	3
Malnutrition	3
Tension pneumothorax	2
General	
Pulmonary embolism	2
Thrombophlebitis	2
Stress ulcers	1
Cardiac arrhythmia	1
	—
Total	14

TABLE 3. *Nontraumatic Chylothorax*

Case	Age Sex	Etiology	Duct Ligation	Result
1	55 F	Tuberculous adenopathy	No	Dead in 4m
2	68 F	Thyroid carcinoma	No	Dead in 3y
3	4 M	Malignant lymphoma	No	Dead in 3m
4	12d F	Idiopathic	No	Cured
5	3m M	Idiopathic	No	Cured
6	1d F	Idiopathic	No	Cured
7	55 F	Thoracic duct anomaly	Yes	Died at Surgery

TABLE 4. *Traumatic Chylothorax*

Case	Age Sex	Etiology	Duct Ligation	Result
8	23 M	Gunshot wound—body T-11	No	Cured
9	54 F	Resection of thoracic aortic aneurysm	No	Died
10	3 F	Blalock procedure	Yes	Cured
11	4 F	Blalock procedure	No	Cured
12	2 F	Division of patent ductus	Yes	Cured
13	41 M	Left radical neck dissection	Yes	Cured
14	22 M	Spinal dislocation—T12-L1	Yes	Cured
15	4m F	Correction of vascular ring	No	Cured

a fibrinous pleural peel were encountered in the right thoracic cavity. The thoracic duct was identified just above the diaphragm deep in the costovertebral angle. A laceration in the center of its exposed portion was emitting a pulsatile flow of chyle. Proximal and distal ligation of the duct was performed and the leak stopped. Follow-up chest x-rays showed no recurrence of the chylothorax (Fig. 2). The postoperative course was uneventful. The patient was discharged from the hospital on June 2, 1971 in a body spica cast for support of his spinal dislocation. He had lost 27,000 cc. of chyle over a 13-day period before surgical correction was performed.

Discussion

Early reviews of chylothorax have adequately documented the results of nonoperative management. Shackelford[5] summarized 41 cases of traumatic chylothorax that had appeared in the literature prior to 1938. Therapy consisted of drainage and dietary adjustments to decrease the flow of chyle. The mortality rate was 48 per cent. The first successful transthoracic ligation of the thoracic duct was performed by Lampson[2] in 1946. The beneficial effect of a direct approach to this problem is well demonstrated by Goorwitch's[1] collection of 31 traumatic cases in 1955. The overall mortality rate was 10 per cent and there were no deaths among the 15 patients who were treated surgically.

Subsequently a number of authors have reemphasized the validity of an initial trial of nonoperative therapy, and have expressed concern that this method was becoming too quickly and unnecessarily replaced by thoracic duct ligation. Maloney and Spencer[3] presented 13 young patients with chylothorax resulting from cardiovascular surgery. Eleven were treated successfully with multiple thoracenteses. Williams and Burford[6] have concluded that surgical intervention is rarely indicated in traumatic cases and often ineffective in nontraumatic cases. This therapeutic controversy in chylothorax seems to stem from an uncertainty as to the exact clinical factors which indicate surgical intervention.

TABLE 5. *Magnitude of Chyle Loss in Traumatic Cases*

Case	Age	Total Volume (ml.)	Nonoperative Period (days)	Aver. Loss (ml./d)	No. of Taps	Duct Ligation
8	23	56,400	49	1100	34	No
9	54	12,000	43	280	24	No
10	3	1,800	7	350	6	Yes
11	4	900	7	130	2	No
12	2	1,500	12	125	3	Yes
13	41	16,100	9	1800	4	Yes
14	22	27,000	13	2000	—*	Yes
15	4 m	110	1	110	1	No

* Continuous tube drainage almost exclusively

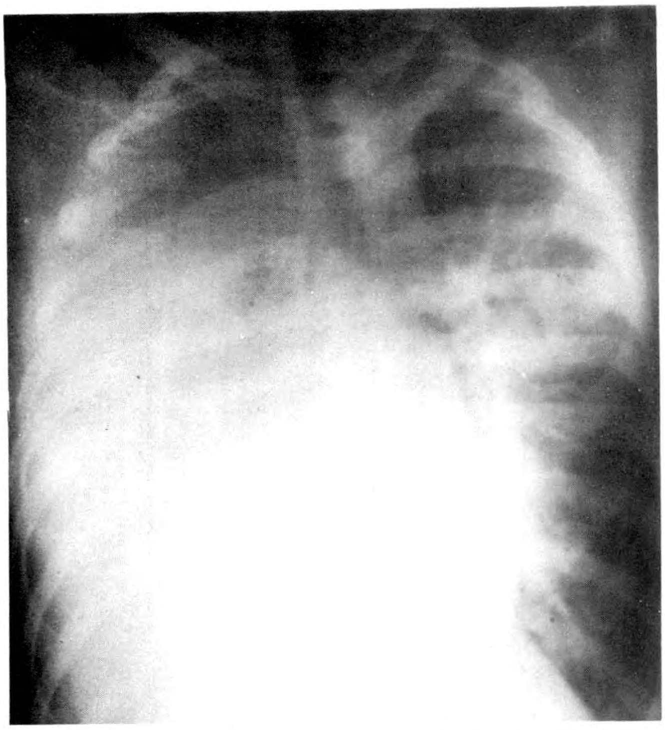

FIG. 1. Supine chest x-ray showing 4000 ml. of right pleural fluid. Note the obliteration of the right hemidiaphragm and the right hilar lucent area representing the almost completely collapsed right lung.

The dangers involved with prolonged nonoperative management relate primarily to the tremendous metabolic deterioration that may occur. The daily volume of thoracic duct flow can approach 2500 cc. with electrolyte and protein concentrations approximating plasma values. Sixty or 70 per cent of ingested fat is conveyed to the blood stream by this route. Therefore the magnitude of fluid, electrolyte and nutrient losses can be great. Replacement of these is compounded by inaccuracy in their measurement. Chest tubes often become obstructed due to the gelatinous disposition of chyle. Frequent thoracentesis can also result in incomplete drainage and may be complicated by the production of hemothorax and/or tension pneumothorax. Additional local intrathoracic problems may result from chyle loculations and fibrosis. Of six patients in the present series in whom examination of the pleural cavity was possible, three demonstrated intrapleural chylous adhesions. One

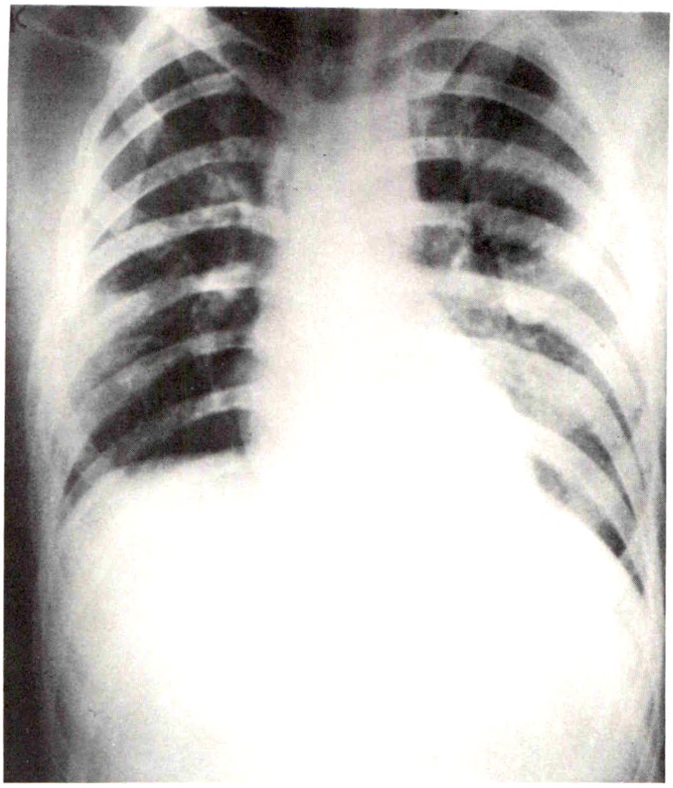

FIG. 2. Postoperative chest x-ray showing complete resolution of the right chylous effusion.

patient (Case 7) eventually died as the result of severe pulmonary constriction due to chylofibrosis. Fortunately intrapleural infection is uncommon due to the bacteriostatic properties of chyle. Negative cultures in all 15 of the cases reported here confirm this feature which is well documented in previous reports.

Some patients, however, demonstrate spontaneous resolution of the chylous effusion without operative intervention and without morbidity. The problem is that of defining those who will require operative intervention, early in their course, before complications occur.

The cases of nontraumatic etiology can usually be managed nonoperatively. Those patients in whom the chylous effusion was due to extrinsic compression of the duct by another disease process all died of that primary disease. Chylothorax was never a major determinant in the medical outcome. In the absence of trauma and exclusive of the neonatal group, chylothorax is an ominous sign, generally signifying widespread mediastinal involvement of a rapidly fatal illness. Operative intervention is usually ineffective and should therefore be avoided. The neonates with idiopathic chylothorax conversely, all responded well to thoracentesis. Randolph and Gross[4] have reported a similar experience with neonatal chylothorax, finding it necessary to operate on only two in a series of 15.

The approach to traumatic chylothorax presents a more difficult therapeutic problem. There is general agreement that an initial trial of nonoperative therapy is indicated. The problem occurs in defining the appropriate situation and time for performing ductal ligation. Two patients in the present series were subjected to excessively prolonged nonoperative management (Table 5). One (Case 8) occurred in 1942 before ligation of the thoracic duct had been successfully performed. The other (Case 9) gradually declined to death, emphasizing that even with slow leaks (280 cc. per day) a prolonged nonoperative approach may be hazardous. A pulmonary embolus delayed operation in another patient (Case 14). With these exceptions a fairly good correlation can be found between patient age, rate of chyle flow, operative intervention, and survival (Table 5). Review of these cases has provided a rough guide for determining when ductal ligation should be considered. A daily chyle flow not exceeding 1500 cc. in adults or 100 cc. per year of age in children is reasonably well tolerated for as long as 5 days. If this rate of flow for this period of time is exceeded, intervention should be strongly considered. Careful observation and frequent chest x-rays are necessary to be certain that the full rate of loss is appreciated. Daily losses should be faithfully replaced intravenously with solutions containing appropriate concentrations of electrolytes and protein.

Summary and Conclusions

The cases of 15 patients with chylothorax treated at the University of Cincinnati Medical Center during the past 29 years are reviewed. A wide variety of causes and a wide range of magnitude of chyle drainage is displayed. Eight cases resulted from trauma. The review was conducted in an attempt to more accurately define the indications for operative intervention. The following has been concluded:

1. Idiopathic cases in the neonate usually respond well to thoracentesis.
2. Nontraumatic chylothorax, exclusive of the neonatal group, usually suggests a widespread fatal illness. Operative intervention is usually ineffective and should therefore be avoided.
3. In cases resulting from trauma an initial trial of nonoperative management is indicated. Transthoracic ligation of the thoracic duct is indicated when:
   a) the average daily chyle loss has exceeded 1500 cc. in adults or 100 cc. per year of age in children for a 5-day period.
   b) the chyle flow has not diminished while approaching 14 days in duration.
   c) nutritional complications appear imminent.

4. Early surgical intervention should especially be considered in traumatic chylothorax in the pediatric age group.
5. Prolonged nonoperative management is endangered by complications specific to chylothorax, as well as those of a general nature.

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Book Reviews

Hemobilia (Biliary Tract Hemorrhage) History, Pathology, Diagnosis, Treatment, By PHILIP SANDBLOM, M.D., Ph.D., Professor Emeritus and Past President, University of Lund, Sweden. With a Foreword by Warren H. Cole, M.D., Professor Emeritus of Surgery, University of Illinois. Charles C Thomas, Publisher, 146 pages, 38 illustrations, $19.75.

IT IS UNUSUAL when a mature monograph is written by the man who introduced the term which embodies the subject. While Professor Sandblom traces the history of hemobilia back to Glisson's paper in 1654, it was Sandblom himself who brought the subject to the attention of surgeons and physicians of this century and who introduced the descriptive term "hemobilia" for a variety of conditions in which blood leaves the circulation and traverses the bile passages.

The book is divided into two parts: Part I gives a definition, including the history, pathology, symptoms, diagnosis and treatment. Part II approaches the subject from the standpoint of etiology and describes the role of trauma, both accidental and iatrogenic, inflammation, gallstones, tumor, and vascular disorders. This is followed by an Appendix, listing a number of unpublished cases of hemobilia, and a thorough Bibliography with both an author index and a subject index for easy reference.

Professor Sandblom has long been one of the best known and most highly regarded of European surgeons in this country, and his scholarly discussions and presentations at the meetings of the American Surgical Association and the Southern Surgical Association are well known to many readers of the *Annals of Surgery*.

The monograph is characteristically thorough and yet clear and succinct. The illustrations are well selected and meaningful. The purpose of the book is beautifully stated in the Epilogue. A portion of which reads as follows:

> Three hundred years have now passed since Francis Glisson showed that bleeding from the digestive tract may originate in the liver or biliary tract. Yet not until our day has this become general knowledge and the syndrome found its way into the textbooks. Hemobilia has now become the currently used term for the condition. As is evident from the more than five hundred cases reviewed in this monograph, the incidence of this syndrome is not rare. Judging from the figures from different periods of time it is also increasing in frequency. . . . This may be due to the fact that more widely disseminated knowledge of the syndrome and improvement in method have meant that fewer cases escape diagnosis today. On the other hand, there may be a genuine increase because of the rising number of traffic accidents which often result in liver injury.
>
> It is depressing to think about all of the patients in the past who were mismanaged or who died because the diagnosis was made too late or missed altogether. Nearly every case chosen to illustrate various points in this book was subjected to one or more inappropriate operations before the true situation was realized. As mentioned, the reason for this is that hemobilia is apparently so uncommon that hardly any clinicians encountering it recognize it from their own experience, and only a few have previous knowledge of it. One is reminded of Coleridge's words: "The light which experience gives us is a lantern on the stern which shines only on the waves behind us."
>
> My aim in writing this book has been to hang a lantern on the bow as well so that by the light of knowledge the clinician may discern the snags and hazards ahead and steer a safe course between them.

Hemobilia is an important reference but unlike so many important references, it is a pleasure to read. Written as it is by the man with whom the term "hemobilia" is so clearly identified, it will be sought by many collectors of landmarks in medicine.

JONATHAN E. RHOADS, M.D.
University of Pennsylvania
School of Medicine, Phila.

Textbook of Operative Surgery, ERIC L. FARQUHARSON, Williams & Wilkins Co., Baltimore, 1972.

THIS IS an outstanding text and I believe one that will have wide and well deserved acclaim. In an era when the publication of detail on surgical problems is so vast that no ordinary physician can read, much less assimilate, all the factual data and accompanying discussion of theory, this is indeed refreshing and delightfully informative. The reader will do well to note the author's preface to the fourth edition, in which he sets forth the objectives that have been pursued in the preparation of this, the fifth edition. Briefly stated, it is to be a one volume book written by a general surgeon to present in balanced perspective operative surgery, and to describe, in detail and with adequate illustrations, all operations that a general surgeon may be called upon to undertake or assist in. The surgical anatomy of the region, the indications for operation based on the pathology presented together with pre- and postoperative management are woven well into each section.

The content of the text is dealt with in 29 sections covering 940 pages. Illustrations and narrative are efficiently arranged so that the reader may at a glance gain a specific detail on a page that he has been guided to by the index. On the other hand, each section provides a comprehensive treatise that is equally considerate of the reader's time.

The material is current and up-to-date, portraying the experience with procedures that have been demonstrated to be most satisfactory for the situation to be dealt with. The melding together of anatomy, physiology, and pathology with surgery has been accomplished in a masterful fashion that renders the book unique. It should be equally satisfying to the general surgeon seeking information pertaining to the surgical specialties and the surgical specialist looking for data for principles of surgery in general and other specialties.

Anatomy and pathology are well integrated with the surgery of the regions. The illustrations are well selected and superbly reproduced. They meld in with the text so that the reader gains a comprehensive view as well as technical detail of the surgical measures portrayed.

The general basic principles applicable to all surgery have been nicely covered in the first section. Operations on the skin and subcutaneous tissues, the sections of operations on muscles and tendons, blood vessels, nerves, bones and joints, hand and fingers precede and prepare the reader for those on wounds of the extremities and amputations. As one proceeds to the sections on regions that define the boundaries of the specialties, the reader becomes aware of the lack of repetition and the simplified direct description of surgical technic.

The section on operations within the thorax, thoracic surgery, both pulmonary and cardiac, is an example of a field of recent developments presented in terms that will be appreciated by both medical student and senior chest surgeon. Undoubtedly the sections that will be utilized most frequently will be those dealing with operations within the abdomen. Because operations upon the biliary tract are done more frequently than any others within the abdomen, it is anticipated that Chapter XX *The Gall Bladder, the Bile Ducts and the Pancreas* will be consulted more often than any other.

While this is truly a surgeon's book, it is much more. For the internist and the diagnostitian who seek to evaluate surgical therapy for their patients' disease or disability, it is a ready and authentic reference from the standpoint of what it entails. In this era of rapid expansion of medical care it is of prime importance to be up-to-date on accepted surgical procedures. This text has done just that.

For those in the early years of medical experience, including medical students, interns and residents in graduate training, it should be most valuable.

All-in-all it is a single volume surgical text without a peer.

DR. FRANK GLENN

Letters to the Editor

June 30, 1972

Dear Dr. Rhoads:

We would like to make some comments on the article "Source of a Lysosomal Enzymes Acid Phosphatase, in Hemorrhagic Shock" by Clermont, Adams and Williams appearing in the *Annals of Surgery* **175**:19–25, 1972. We have read with interest this paper as we ourselves have done work in this field and published it several years ago/Barankay, T. *et al.*: Changes in the Level of Lysosomal Enzymes in Plasma and Lymph in Hemorrhagic Shock. *Medicina Experimentalis* **19**:267–271, 1969. Our results do not agree with those of Clermont and co-workers. They do not make reference to our work but we are not surprised by that as we all are aware of the difficulties of searching the large literature.

We are only surprised by the interpretation of their own data by these authors with the apparent agreement of your reviewers. Clermont and co-workers claim that the major route of entry of acid phosphatase into the blood plasma in shock is via the lymphatics. When lymph flow was diverted during shock rise in plasma acid phosphatase activity was less than in the controls. They write, p. 23. second column, paragraph 1: "As shock continued pH fell and mucosal cell resistance was overcome, lymph acid phosphatase rose steeply to 796% above control, while serum acid phosphatase only increased 359%. This indicates that although some enzymes enter the splanchnic circulation directly, the major route is indeed via the lymphatics." Examination of Table 1. and the text on methods, however, reveals that acid phosphatase levels in plasma are given in milliunits/ml., basically a concentration, while lymph values are given in milliunits/30 min., *i.e.* total output during a time period. Unfortunately such important parameters as bleeding volumes are missing. If we assume that the average plasma volume of their dogs was 1000 ml., assuming a plasma volume of 50 ml./Kg. for a 20 Kg. dog, and this was reduced to 500 ml. at 240 minutes by the shock procedure, we can simply calculate the expected enzyme activity in the plasma at this time from the data in Table 1, had the total amount of enzyme carried by the lymph reached the circulation during this period, as it did in the controls. The total content of acid phosphatase in lymph till reinfusion was 282.9 milliunits in Group II. This was obtained by adding the lymph enzyme contents up to 240 minutes as given in Table 1. If we assume that this amount of enzyme is added to the plasma volume, 500 ml., at this time and it would be distributed only in the plasma, the latter is a very optimistic assumption. Then the resultant change in plasma enzyme concentration would be 0.56 milliunits/ml. or to 9.25 milliunits/ml. instead of 8.69 milliunits/ml. This is still far from the 19.19 milliunits/ml. of Group I, and one must assume that some factor other than lymph diversion is responsible for this difference between the two groups. Even if we assume a circulating plasma volume of only 250 ml. at the time of reinfusion, addition of lymph enzyme content to the plasma would account only for about 10% of the difference in plasma activities between the two groups.

If, however, the severity of the shock, characterized by the bleeding volume and its time distribution, was lower in Group II than in Group I, this could easily explain the difference in plasma enzyme activities as we know that the rise in plasma lysosomal enzyme activities parallels the severity of the shock.

The same could be true for the two enterectomy groups but we refrain to speculate on the results of experiments done on three animals only.

Sincerely yours,
Dr. S. Nagy
Dr. T. Barankay
University Medical School
of Szeged,
Szeged, Hungary

December 21, 1972

Dear Dr. Rhoads:

I would like to reply to the comments made by Drs. S. Nagy and T. Barankay regarding our paper "Source of Lysosomal Enzymes Acid Phosphatase, in Hemorrhagic Shock" published in *Annals of Surgery* **175**:1919, 1972.

As the title of the paper indicates, the primary purpose of our study was to determine the source of serum acid phosphatase activity in hemorrhagic shock and in this regard, to define the quantitative contribution by the intestine. Drs. Nagy and Barankay seem to be in disagreement with a secondary part of the study which has to do with the means by which the enzyme reaches the serum.

In our study, both the control and lymph drained animals were subjected to the same standard shock and the severity of shock in the two groups was essentially the same as evidenced by comparable changes in serum lactate, pyruvate and pH. Since the increase in serum acid phosphatase levels was less in animals subjected to lymphatic diversion, with all other things equal, we considered it valid to conclude that this difference was the result of thoracic duct drainage. Our conclusion is not original or unique. Berman *et al.* (*Annals of Surgery* **169**:202, 1969) showed a 60% decrease in peak serum acid phosphatase levels in dogs subjected to hemorrhagic shock following thoracic duct drainage as compared to non-lymph drained dogs (from .49 to .2 Sigma units/ml), a change very similar to that which we found in our study. Dumont and Weissman (*Nature* **201**:1231, 1964) studied Beta glucuronidase activity (which parallels acid phosphatase activity in shock) and noted that the serum levels in control animals were significantly greater than those in experimental dogs with thoracic duct diversion. They concluded that the lysosomal enzyme "Beta glucuronidase gains excess to the circulation primarily via the lymphatic route."

Admittedly, there appears to be a discrepancy in our report between the total enzyme content of diverted lymph and the resulting decrease in serum concentration. However, the values as recorded represent enzyme content per Kg. weight as calculated from the flow values which were expressed in ml/Kg. We apologize for not making this clearer. It means that the mean total lymph enzyme value per animal would be approximately 20 times greater or that about 5,650 milliunits of enzyme was diverted after 240 minutes instead of 282.9 milliunits. Distributed over a realistic plasma volume of 750 ml, this would be about 7.5 milliunits/ml. If this amount of enzyme had not been diverted, it would have resulted in a serum acid phosphatase concentration of about 16 milliunits/ml or close to the figure of 19 milliunits/ml noted in the group without lymph drainage. Our method of reporting lymph enzyme content was to avoid large numbers. Regardless of the confusion created, our conclusion is the same, that is, that a major part of acid phosphatase reaches the serum via the lymphatics.

We apologize for overlooking the commentors paper (*Medicine Experimentalis* **19**:267, 1969) when researching the literature on this subject. I have since examined their report in which they conclude that "lymph does not play a major role in the transport of lysosomal enzymes in shock." They based this statement on their findings that 1) enzyme continued to reach the plasma even though thoracic duct lymph was diverted, and 2) plasma levels of enzyme were always higher than lymph levels at corresponding time intervals.

With regards to their first reasoning, it should be pointed out that we too found that plasma enzyme content increased in dogs with thoracic duct diversion and proportionately to about the same extent which they found. However, the increase in plasma levels was significantly greater in dogs without a lymph fistula at corresponding time intervals. (We estimated that approximately 60% of the enzyme reached the plasma via the thoracic duct, the remainder via another route). The *difference* in plasma enzyme level between lymph drained and non-drained dogs is the all important factor in evaluating the relative contribution of the lymphatics to enzyme transport. Since Drs. Nagy and Barankay failed to study dogs without a lymph fistula, they had no controls for comparison and therefore no basis for making any conclusions.

Their second reasoning is also open to criticism. In their report, they expressed lymph enzyme as concentration rather than total content and thus failed to consider that lymph volume is at least three times plasma volume (approximately 15% body weight vs 5% body weight). If they had applied this factor to their data then lymph enzyme content would have been *greater* rather than less than plasma enzyme content at corresponding time intervals.

Finally, we would like to say that four references were included in our article which support our conclusion that a major part of lysosomal enzymes in shock reach the circulation via the lymphatics. The paper by Drs. Nagy and Barankay is the only one that I am aware of that states a contradictory opinion.

Thank you for allowing us to present this rejoinder.

Sincerely yours,
James T. Adams, M.D.
Associate Professor of Surgery
Strong Memorial Hospital,
Rochester, New York

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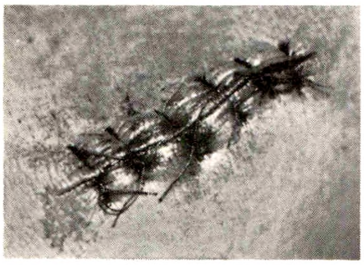

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